SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF FLUORINATED HALLUCINOGENIC TRYPTAMINE ANALOGS AND THIENOPYRROLE BIOISOSTERES OF *N,N*-DIMETHYLTRYPTAMINE

A Thesis

Submitted to the Faculty

of

Purdue University

by

Joseph Bernard Blair

In Partial Fulfillment of the

Requirements for the Degree

of

Doctor of Philosophy

August 1997

To...

my Mom, Rachel Marie Blair

my wife, Suwanna

and my daughter, Tiffany Marie

ACKNOWLEDGMENTS

Most importantly, I would like to thank my major professor, Dr. David E. Nichols for believing in me, and for teaching me how to be a good researcher and a good graduate student. Dr. Nichols regularly provided me with encouragement and gave me answers and critical advice to solve the problems that arose during the syntheses of the compounds in this thesis. He taught me a huge amount of chemistry, many times more than I learned in any class, and made me realize the rewards of working hard and being efficient in the laboratory. Dr. Nichols is not only an excellent chemist and pharmacologist but also an excellent manager of a research group by fostering an environment of hard work, diversity, and cooperation.

I would like to thank Professors Mark S. Cushman and Gary E. Isom for serving on my advisory committee and Professor Donald E. Bergstrom for serving on my advisory committee and advising me on my second year seminar. Also, Professors James E. Robbers and Jerry L. McLaughlin were my teaching assistant bosses and I appreciate their guidance in these duties, which was an experience I enjoyed very much.

I wish to express my sincere thanks to the members of the Nichols' group. The Nichols group is typically very diverse, with members during my five years in the group originating from South Korea, Switzerland, Italy, Jordan (Palestinian), United States, India, Poland, Germany, Thailand, Puerto Rico, Russia, Ethiopia and China. It is truly an international environment and we all learned a great deal about each other's customs, lifestyles, and countries.

Individually, I would like to thank Stewart Frescas for his help, especially my first two years, and for teaching me indole chemistry. Dr. Martin Doll and I developed a very close friendship in a short time, one that I know will last a lifetime, and I appreciate all of his support and advice that got me through some of the difficult days. Matt Parker provided me with many ideas for my projects and much insight into chemistry, mechanisms, and life in general. I especially enjoyed the flight to Chicago with Matt piloting, including the "zero-G" maneuver.

Sungkyung Lee and I took all of the same classes together and joined the Nichols group at the same time. She is one of the nicest persons I know, and I have greatly appreciated her friendship. Amjad Quandil and I had several very interesting conversations, and I am thankful for his friendship. I wish to express my appreciation to Dr. Debasis Ghosh for putting up with me for two years as a lab partner, and for lively discussions about world politics.

Danuta Marona-Lewicka performed the behavioral studies with the help of Debbie Kurrasch. Denuta is one of the hardest working persons I have ever met. She always seemed to be doing several studies at once and made a big effort in recent weeks to provide me with as much information as possible, including the behavioral graphs and data which she produced and gave me on disk for easy inclusion into this thesis. She also taught me a great deal about the principles and procedures involved in the behavioral testing and pharmacology of hallucinogenic compounds in general. I would also like to thank Arthi Kanthasamy for doing the preliminary radioligand competition studies so I

would have some initial data for my thesis, even though she was very busy with her classes and exams.

I wish to thank Mohammad Ahmadian and Maneesh and Shilpa Pingle for their friendship throughout the past five years. Mohammad and I especially supported each other during difficult semesters, while Maneesh and I wore out about every pool table in town our first year or two at Purdue. A special thanks goes out to the members of Barnacle Spöre: Chris Colbert (lead singer), Tom Klem (drums), Greg Taylor (lead and rhythm guitar), Nate Jones (bass), and Nick Oberlies (rhythm guitar).

I would like to thank my wife Suwanna for her patience and encouragement during the last two years while we were apart. In our first year of marriage we only spent a total of two months together, and I know it was as difficult on her as it was on me. I am also very appreciative that she took care of me this last month, and for her assistance in writing the experimental portion. I could not have done it in such a short time without her. I would also like to thank my daughter Tiffany for keeping me young and for her beautiful smile. She is (of course) the most wonderful and smartest little girl in the world, and I am so very proud of her. I also wish to thank all of my brothers and sisters in the Blair family (Bill, Keith, Bear, Ernie, Bob, Karen, and Shiloe) who all at one time or another throughout my college years helped me out and were very supportive of my educational goals.

Finally, I wish to thank my mother, Rachel Marie Blair, who raised eight children by herself (the father was absent). When we were young, we did not have many material things, but we had a home, food, and lots of love. She took any job, including manual

labor, to put that food on our table. Later, she made use of her best skill: providing love and caring to children, by opening a very successful day care center called "The Children's Corner" in Ada, Minnesota, in which she cared not only for happy children, but also children from troubled homes in conjunction with the welfare department as a foster home. It took its toll on her health, but she did it because she cared about children. My mother never insisted I do well in High School or obtain a college degree, much less a graduate degree, but she always encouraged me to work hard (by setting an example herself), and was a pillar of support only a phone call away whenever I needed it. Thanks Mom.

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LIST OF ABBREVIATIONS

Ar = aromatic

brine = saturated aqueous sodium chloride

^{o}C = degrees centigrade

CIMS = chemical ionization mass spectrometry

CNS = central nervous system

conc = concentrated

DD = drug discrimination

DET = *N,N*-diethyltryptamine

DMF = dimethyl formamide

DMSO = dimethyl sulfoxide

DMT = *N,N*-dimethyltryptamine

DOB = 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane

DOI = 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane

DOM = 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane

DOTFM = 1-[2,5-dimethoxy-4-(trifluoromethyl)phenyl]-2-aminopropane

ED_{50} = dose at which 50% of the test animals selected the drug lever in the two lever DD assay

eq = equivalent(s)

g = gram(s)

h = hour(s)

5-HT = 5-hydroxytryptamine, serotonin

ip = intraperitoneal

LAH = lithium aluminum hydride

LSD = lysergic acid diethylamide

M = molar

MAO = monoamine oxidase

μg = microgram(s)

mg = milligram(s)

min = minute(s)

mL = milliliter(s)

mmol = millimole(s)

mp = melting point

m/e = mass to charge ratio

N = normal

NE = norepinephrine

nM = nanomolar

NMR = nuclear magnetic resonance spectrometry

8-OH-DPAT = 8-hydroxy-2-(di-*n*-propylamino)tetralin

SAR = structure-activity relationship(s)

TLC = thin layer chromatography

TMD = transmembrane domain

ABSTRACT

Blair, Joseph Bernard. Ph.D., Purdue University, August 1997. Synthesis and Pharmacological Evaluation of Fluorinated Hallucinogenic Tryptamine Analogs and Thienopyrrole Bioisosteres of *N,N*-Dimethyltryptamine. Major Professor: David E. Nichols.

A series of fluorinated tryptamine analogs of the hallucinogenic compounds DMT, DET, Psilocin, and 5-methoxy-DMT was synthesized to investigate why 6-fluoro-DET is inactive as a hallucinogen, and to determine the effects of fluorination in the molecular recognition of these compounds at serotonin receptor subtypes. The target compounds were evaluated using *in vivo* behavioral assays for hallucinogen-like and 5-HT_{1A} activity, and *in-vitro* radioligand competition assays for their affinity at 5-HT_{1A} receptor sites. Hallucinogen-like activity, evaluated in the two-lever drug discrimination paradigm using LSD-trained rats, was attenuated or abolished for all of the fluorinated analogs. The tryptamine, 4-fluoro-5-methoxy-DMT **11**, displayed high 5-HT_{1A} activity in both assays, with potencies comparable to the standard 5-HT_{1A} full agonist 8-OH-DPAT. The ED_{50} of **11** in the two-lever drug discrimination paradigm using LY293284-trained rats was 0.17 μmol/kg, and the K_i at [^{3}H]-8-OH-DPAT-labeled 5-HT_{1A} receptors was 3.8 nM. The results indicate that fluorination of hallucinogenic tryptamines generally attenuates 5-HT_2 and 5-HT_{1A} receptor affinity, with the notable exception of 4-fluoro-5-methoxy substitution, which may involve a novel mechanism in the molecular recognition of tryptamines at serotonin receptors. The hypothetical formation of a hydrogen bond involving the 4-fluoro substituent in the 5-HT_{1A} receptor pocket is discussed. The

thienoypyrrole positional isomers 6-[2-(*N*,*N*-dimethylamino)ethyl]-4*H*-thieno[3,2-*b*]pyrrole **12** and 4-[2-(*N*,*N*-dimethylamino)ethyl]-6*H*-thieno[2,3-*b*]pyrrole **13** were synthesized as bioisosteres of DMT.

INTRODUCTION

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter with numerous physiological functions in the central and peripheral nervous systems. The structure of serotonin (Figure 1) was elucidated in 1949[1] after its isolation from blood serum and the discovery that it had potent vasoconstrictor properties.[2] Serotonin was subsequently identified in brain tissue.[3] In 1955 Brodie *et al.*[4] provided information about serotonin's role in brain function by demonstrating that the sedation produced by reserpine was linked to the depletion of brain serotonin. In 1963 it was shown that serotonin could have both excitatory and inhibitory properties in the central nervous system.[5]

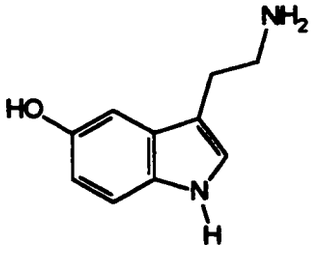


Figure 1. The neurotransmitter serotonin

Serotonin neurons mostly originate from the raphé nuclei in the brainstem, but serotonin nerve terminals are widely distributed throughout the brain.[6] Higher concentrations of serotonin are found in the hypothalamus, with lower concentrations in

the cortex. While only 1-2% of the total serotonin in the body is found in the brain, the pineal gland has the highest concentration of any known animal tissue.

Hallucinogenic Substances

Naturally occurring hallucinogenic substances have been used for millennia by many societies in their religious and medicinal practices. The first report of the ceremonial use of hallucinogenic mushrooms in Mexico was by the Spaniards after the conquest.[7] The Aztecs called them *Teonanacatl* meaning "sacred mushroom" or "God's flesh".[8] Mushroom stones sculpted in images that are part animal (or human) and part mushroom, dated about 1000 B.C., have been found throughout Southern Mexico and Central America.[7] Today, descendants of the Mayans continue to use these mushrooms for ceremonial purposes.

The hallucinogenic peyote cactus is used by members of the Native American Church for religious purposes. Also, *Ayahuasca* is a hallucinogenic drink prepared from a South American vine (*Banisteria cappi*) used by a religious order in Brazil. This decoction is made from the root of the plant. In each culture, the respective plant or substance is held in high reverence and used cautiously by, or in the presence of, experienced persons. The effects of hallucinogens can include increased body temperature, pupil dilation, pilomotor erection, pleasant feelings or anxiety, muscle weakness (may be more psychological in nature), drowsiness, visions of altered shapes and colors, and a perception of distorted time.[7] Hallucinogens can produce a "dream-like" state sometimes described as a religious experience. In spite of producing dramatic

changes in perception, these materials are practically nontoxic, the only detrimental side effects typically being psychological or physical injury resulting from experimentation in an uncontrolled environment.

In modern society, however, the possession or use of these plants, the active constituents, or derivatives thereof has been made illegal. Their use has evolved into a recreational one, probably exacerbated by their illegal status. Research has also been hindered, being mostly limited to structure-activity evaluations based on animal models and *in vitro* receptor binding assays of synthetic derivatives. Clinical studies have been rare in the last two decades. Very little is actually understood about the brain mechanisms involved in producing hallucinations. For compounds that have such a profound effect on our perception of this world, much more information is needed.

Hallucinogenic agents are known to interact primarily with serotonin receptors, and an understanding of this neurotransmitter and its receptor system is essential in determining the mechanisms involved in hallucinogenesis. Serotonin is involved in a variety of physiological functions including learning and memory, pain, behaviors such as aggression, neuroendocrine regulation, motor activity, and biological rhythms. Investigation of serotonin receptor ligands will also aid in our understanding of nervous system disorders involving appetite, thermoregulation, sexual behavior, sleep, psychosis, anxiety, and depression,[9] along with processes in the brain that lead to our state of consciousness and perception of the world around us.

Structure-Activity Relationships (SAR) of Tryptamines

Early studies were aimed at identification of the active constituents of psychotropic plants and the evaluation of structure-activity relationships. *Psilocybe* mushrooms were found to contain psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine) and its phosphoryloxy derivative psilocybin (Figure 2). The active constituent of peyote cactus is mescaline (3,4,5-trimethoxy-phenethylamine, Figure 2). *Piptadenia peregrina*, used today by Central American Indians to make psychotropic cohoba snuff, was found to contain several tryptamines including *N*,*N*-dimethyltryptamine (DMT), 5-methoxy-DMT, and bufotenin (5-hydroxy-DMT) (Figure 2).[10]

In evaluation of the activity of these natural compounds, it was found that the 5-methoxy and 4-hydroxy substituents resulted in increased potency over unsubstituted DMT.[10] Later it was found in synthetic derivatives that substitutions on the aromatic ring of tryptamines in the 6- or 7-position abolish hallucinogenic activity, even with a relatively small fluorine atom in the 6-position (discussed later). Substitution is limited to 4- or 5-oxygenation for maximum activity.

Hallucinogenic tryptamines lack oral bioavailability, with the notable exception of psilocin and psilocybin, which seem to resist oxidative metabolism by the liver after absorption from the gastrointestinal tract. Also, the side chain of psilocin may interact with the 4-hydroxy to increase the molecule's lipid solubility and passage into the central nervous system, or adopt an "LSD-like" conformation.[11] LSD (lysergic acid diethylamide) is one of the most potent serotonin receptor ligands known, and may be thought of as a

rigid analog of the tryptamine pharmacophore. However, LSD has a complex pharmacological profile, with affinity not only for serotonin receptors, but other receptor systems including the dopamine D_1 and D_2 receptors and α-adrenergic receptors.

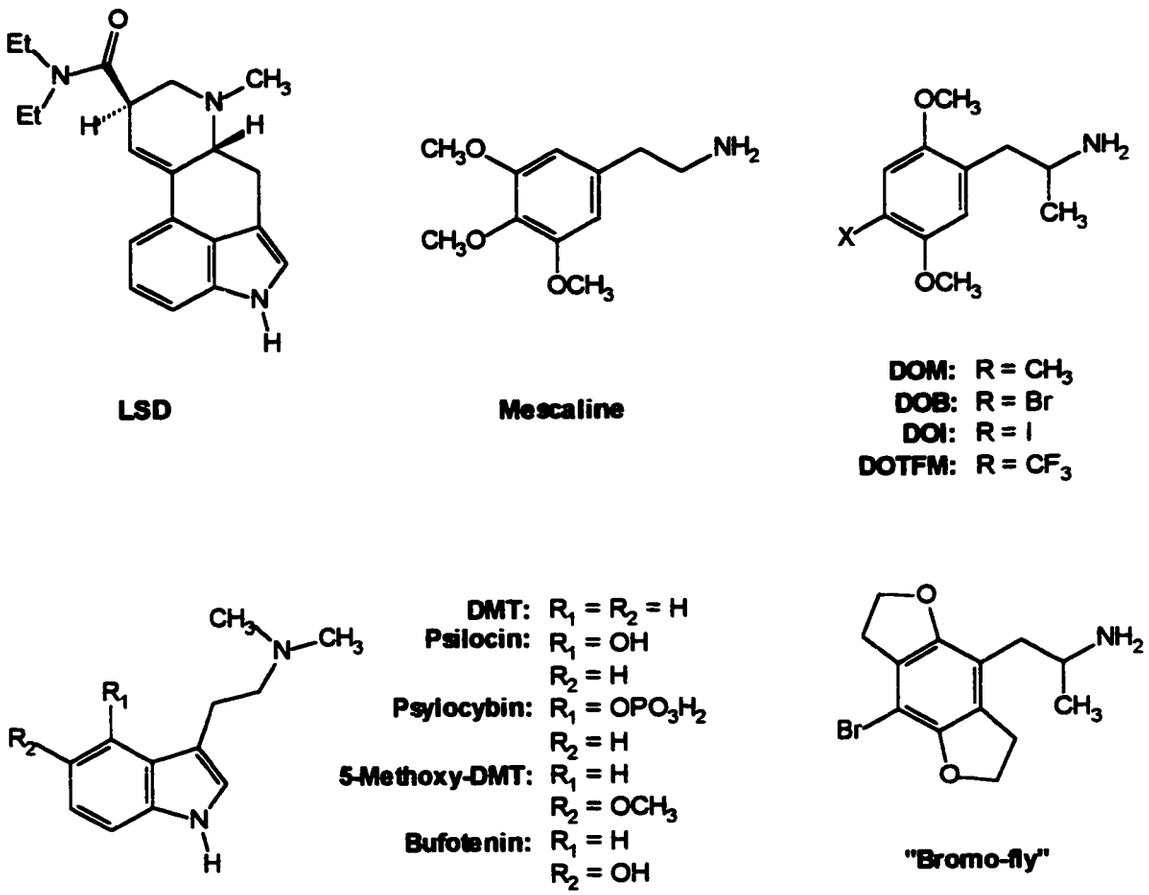


Figure 2. Hallucinogenic compounds and their derivatives.

More recently, it was found that serotonin receptors recognize stereochemical differences in the aminoethyl side chain of tryptamines. Macor *et al.*[12] synthesized analogs of 5-methoxy-DMT with the side chain amine cyclized into pyrrolidine rings, producing a stereogenic center at the carbon α to the amine (Figure 3). The *R* enantiomer has affinity nearly equal to serotonin, while the *S* enantiomer has approximately 20-fold less affinity for 5-HT_{1A} and 5-HT_2 receptors.

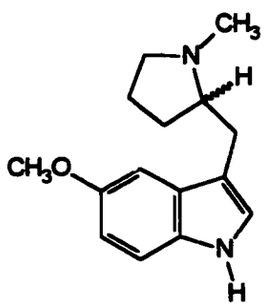


Figure 3. Rigid analogs of 5-methoxy-DMT synthesized by Macor *et al.*[12]

Molecular Recognition at 5-HT_{1A} and 5-HT_2 Serotonin Receptors

The variety of physiological functions of the neurotransmitter serotonin (discussed earlier) is due in part to multiple serotonin receptor subtypes. Most are G-protein coupled (5-$HT_{1,2,4,6,7}$), while the 5-HT_3 is a ligand-gated ion channel.[13] The 5-HT_1 and 5-HT_2 receptors are further divided into several subtypes.[14] The classification of serotonin receptors is outlined in Table 1.[15] G-protein coupled receptors have seven transmembrane

domain (TMD) regions consisting of stretches of hydrophobic amino acid residues (see figure 4). Little is actually known about the 3-dimensional structure of serotonin receptor proteins.

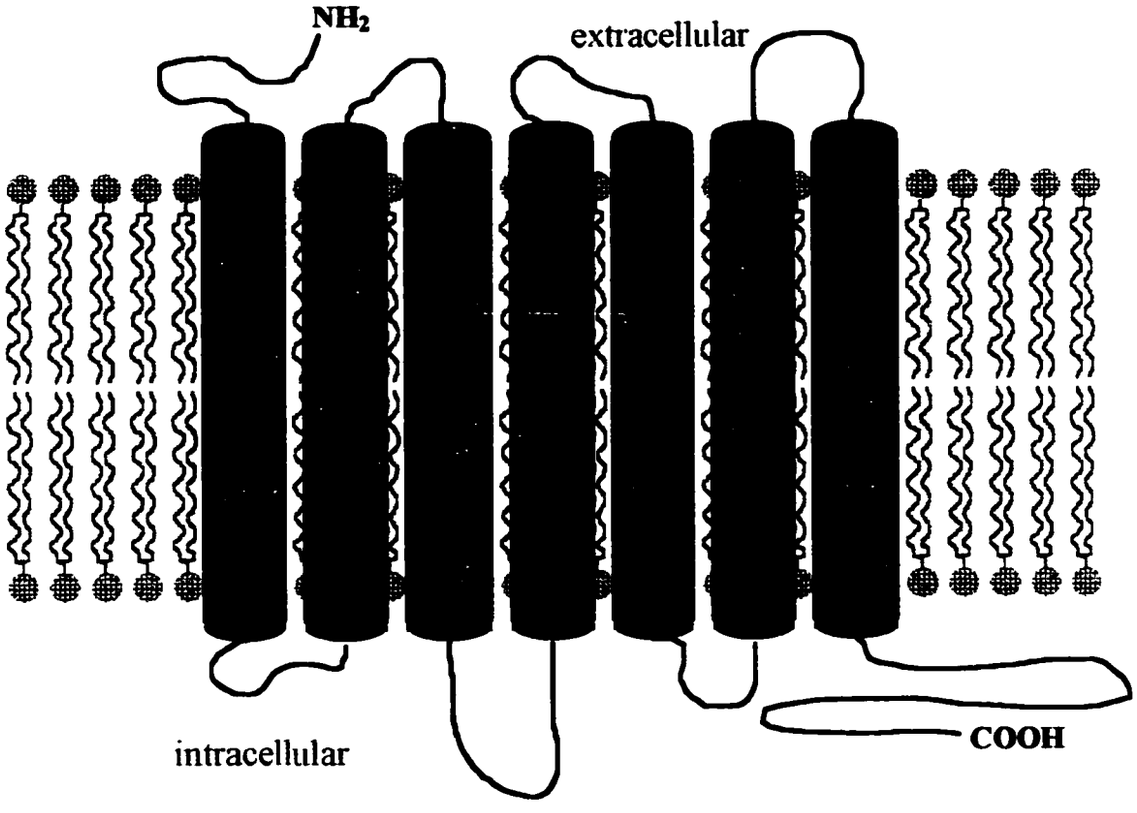


Figure 4. G protein-coupled receptor with seven TMD regions.

Several favorable forces are probably involved in ligand binding, including electrostatic, hydrogen bonding, hydrophobic, van der Waals, and desolvation of receptor and ligand. Electrostatic interactions include not only ionic attractions, but also π-cation interactions involving an aromatic group, or interaction with a fixed dipole, such as an amide bond.[16] Hydrophobic forces may include edge-to-face or offset stacking between

aromatic systems. Unfavorable effects produced upon ligand binding that require energy include 1) conformational changes in the receptor, loss of 2) translational and rotational entropy, 3) internal rotations of ligand, and 4) solvation energy of ligand and receptor.[16]

TABLE 1. Classification of Serotonin Receptors.[15]

Nomenclature	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{1E}
Previous name	--	5-$HT_{1D\beta}$	5-$HT_{1D\alpha}$	--
Selective agonists	8-OH-DPAT	sumatriptan	sumatriptan	--
Selective antagonists	WAY100635 spiperone	GR55562	--	--
Radioligands	[^{3}H]8-OH-DPAT [^{3}H]WAY100635	[^{125}I]GTI [^{3}H]sumatriptan	[^{125}I]GTI [^{3}H]sumatriptan	[^{3}H]5-HT
Effector pathways	cAMP	cAMP	cAMP	cAMP

8-OH-DPAT, 8-hydroxy-2-di-(*n*-propylamino)-tetralin; **GTI**, 5-O-carboxamidoethylglycyl[^{125}I]tyrosinamide-tryptamine; **WAY100635**, *N*-(2-(4-(2-methoxyphenyl)-1-peperazinyl)ethyl)-*N*-(2-pyridyl)-cyclohexanecarboxamide trichloride; **GR55562**, (3-[3-(dimethylaminopropyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]-benzamide

TABLE 1, continued

Nomenclature	5-HT_{1F}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}
Previous name	$5\text{-HT}_{1E\beta}$ 5-HT_{6}	5-HT_{2}	5-HT_{2F}	5-HT_{1C}
Selective agonists	LY334370	DOI α-methyl-5-HT	DOI α-methyl-5-HT BW723C86	DOI α-methyl-5-HT
Selective antagonists	--	ketanserin MDL100907	SB200646 SB204741	mesulergine SB200646
Radioligands	[^{125}I]LSD [^{3}H]LY334370	[^{125}I]DOI [^{3}H]ketanserin	[^{3}H]5-HT	[^{3}H]mesulergine [^{125}I]DOI
Effector pathways	cAMP	IP_3/DG	IP_3/DG	IP_3/DG

LY334370, 4-Fluoro-*N*-[3-(1-methyl-4-piperidinyl)-1*H*-indole-5-yl]-benzamide; **DOI**, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; **BW723C86**, 1-[5(2-thienylmethoxy)-1*H*-3-indolyl]-propan-2-amine hydrochloride; **SB200646**, *N*-(1-methyl-5-indolyl)-*N'*-(3-pyridyl)urea hydrochloride; **SB204741**, *N*-(1-methyl-5-indolyl)-*N'*-(3-methyl-5-isothiazolyl)urea

TABLE 1, continued

5-HT_3	5-HT_4	5-HT_5	5-HT_6	5-HT_7
5-HT_M (peripheral)	--	$5\text{-HT}_{5A,5B}$ (mouse)	--	--
2-methyl-5-HT *m*-chlorophenyl-biguanide	BIMU8 R567506 ML10302	--	--	--
tropisetron ondansetron granisetron	GR113808 SB204070	--	--	--
[^{3}H]zacopride [^{125}I]zacopride	[^{3}H]GR113808 [^{125}I]SB207710	[^{125}I]LSD [^{3}H]5-HT	[^{125}I]LSD [^{3}H]5-CT	[^{125}I]LSD [^{3}H]5-HT [^{3}H]5-CT
internal cation channel	cAMP	unknown	cAMP	cAMP

GR113808 [1-[2-[(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl-1-methyl-1*H*-indole-3-carboxylate; **BIMU8** (endo-*N*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-isopropyl-2-oxo-1*H*-benzimidazole-1-carboxamide hydrochloride; **R567506** 1-(4-amino-5-chloro-2-methoxy-phenyl)-3-(1-*n*-butyl-4-piperidinyl)-1-propanone; **ML10302** 2-(1-piperidinyl)ethyl-4-amino-5-chloro-2-methoxybenzoate; **SB204070** 1-butyl-4-piperidinylmethyl)-8-amino-7-chloro-1-4-benzoioxan-5-carboxylate; **5-CT** 5-carboxamidotryptamine

5-HT_2 Receptor

Known hallucinogenic compounds have high affinities for the 5-HT_{2A} and 5-HT_{2C} receptors, while 4-oxygenated derivatives (such as psilocin) are selective for the 5-HT_{2A} receptor. The 5-oxygenated tryptamines (bufotenin, 5-methoxy-DMT) have approximately equal potency at 5-HT_{1A} and 5-HT_{2A} receptors. Ring substitution in the 6- or 7-positions attenuates affinity for both receptors.[17]

Human	Rat	TMD
Ala^{82}	Thr^{82}	1
Val^{150}	Ile^{150}	3
Ser^{242}	Ala^{242}	5

Figure 5. Differences in sequence homology of the TMD regions of human versus rat 5-HT_{2A} receptors.

The 5-HT_{2A} receptor seems to have at least 3 key features in the recognition site, as indicated by site-specific mutation data from cloned receptors. Most likely, an Asp^{155} in TMD 3 binds the charged aliphatic amine, Ser^{203} in TMD 4 binds the indole NH, and Ser^{239} in TMD 5 forms a hydrogen bond with a 5-oxygen.[12] It was found that psilocin (with a 4-hydroxy) has a 15-fold increase in its affinity for human versus the rat 5-HT_2

receptor. Bufotenin (with a 5-hydroxy) bound both with nearly equal affinity. The human and rat 5-HT_{2A} receptors differ in their sequence homology in the TMD regions by three amino acids as shown in Figure 5. Gallaher and coworkers[18] suggested the selectivity of psilocin could be attributed to the Ser^{242}/Ala^{242} difference in TMD 5. The 4-hydroxy of psilocin is better situated to bind Ser^{242} of the human receptor, which is an alanine in the rat. It was suggested that the 5-hydroxy of bufotenin binds the Ser^{239} instead (see Figure 6), and is not affected by the change $Ala^{242} \rightarrow Ser^{242}$.

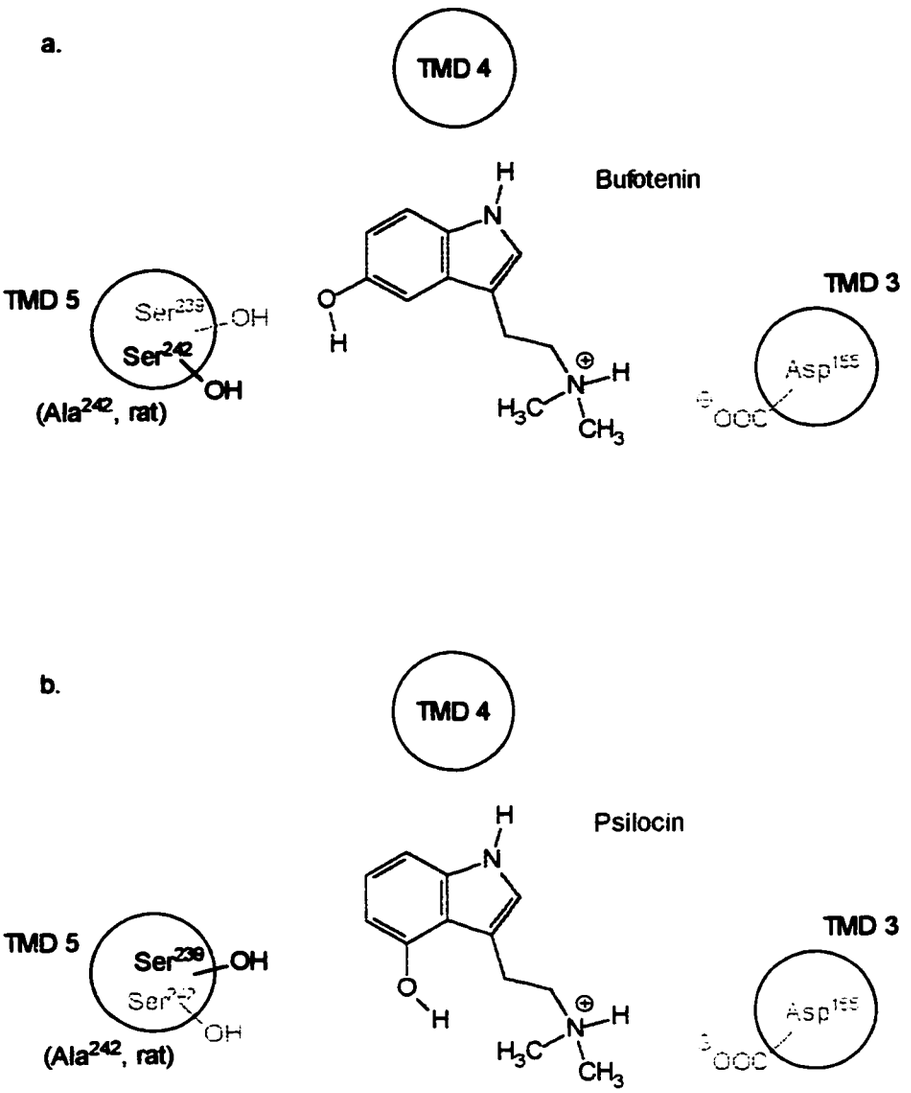
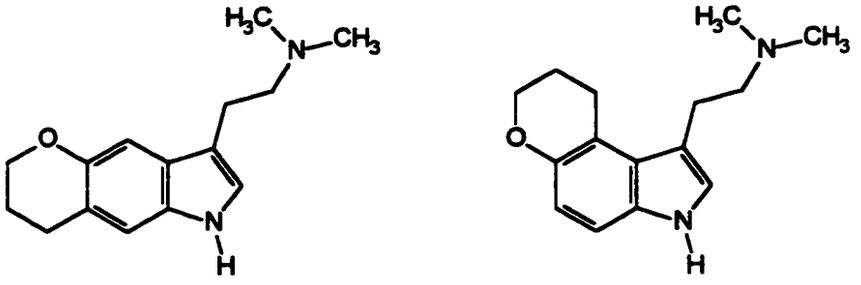


Figure 6. Proposed binding at the human 5-HT_{2A} receptor.[18]

Other researchers have suggested, however, that Ser^{242} of the human 5-HT_{2A} receptor may form a hydrogen bond with N(1)H of unsubstituted ergolines and tryptamines, which have increased affinity for the human 5-HT_{2A} receptor and decreased affinity for the rat 5-HT_{2A} receptor.[19] The change $Ala^{242} \rightarrow Ser^{242}$ (rat→ human) results in the addition of a hydrogen bond donor and acceptor and also increases the steric size of this amino acid residue. Although it is not known how tryptamines bind to the 5-HT_{2A} receptor, the two studies seem to support a ~180° flip of the molecule in binding at the same site.

Macor *et al.*[20] synthesized derivatives of serotonin with the lone electron pairs of oxygen at the 5-position rotationally confined. The dihydropyrano[2,3-*f*]indole derivative (Figure 7a) had very low potency at 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} serotonin receptors. This was suggested to be due, at least in part, to an unfavorable hydrogen bond interaction with the oxygen in this conformation. The dihydropyrano[3,2-*e*]indole (Figure 7b) displayed decreased 5-HT_{1A} activity, but increased affinity for 5-HT_{2A} and 5-HT_{2C} receptors. The authors suggested the low affinity for the 5-HT_{1A} receptor may be due to steric hindrance, inhibiting the aminoethyl side chain from adopting an LSD-like conformation. Modeling also suggested this conformation was indeed unfavorable. The authors concluded that the 5-hydroxy of serotonin acts as a hydrogen bond acceptor at the 5-HT_2 receptor, possibly interacting with a serine or threonine.



(a) (b)

Figure 7. Tetrahydropyrano derivatives of serotonin synthesized by Macor *et al.*[20]

Also, Choudary *et al.*[21] suggested that agonists and certain ergot derivatives interact with Phe^{340} in TMD 6 of the 5-HT_2 receptor. The single point mutation $Phe^{340} \rightarrow Leu^{340}$ produced significant changes in binding properties: 1) [^{3}H]mesulergine (an antagonist) binding was abolished, 2) [^{125}I]DOI (an agonist) binding was abolished, and 3) the ability of the receptor to cause phosphoinositide hydrolysis with the agonists 5-HT, MK212, bufotenin, and quipazine was attenuated or abolished. The binding of the antagonist [^{3}H]ketanserin was diminished only by a $Phe^{339} \rightarrow Leu^{339}$ mutation, which did not affect agonist binding.

In comparison to the tryptamines, studies of amphetamine analogs based on the parent compound mescaline have yielded significant information about the binding of this class of compounds to serotonin receptors. Analogs with 2,5-dimethoxy substitution and a hydrophobic substituent in the 4 position (DOM, DOB, DOI, DOTFM, Figure 2) had higher affinity than mescaline.[22] Monte and coworkers[23] synthesized cyclized derivatives with the 2- and 5-methoxys incorporated into dihydrofuran rings. The most potent

derivative was the tetrahydrobenzodifuran isopropylamine "bromo-fly" (see figure 2), which was selective with nanomolar affinity for the 5-HT_{2A} receptor, while having only low affinity for the 5-HT_{1A} receptor. The substituents important for molecular recognition of amphetamine analogs include a primary amine located two carbons from the aromatic ring, 2- and 5- hydrogen bond acceptors such as oxygen, and a hydrophobic 4-substituent. The α-methyl probably increases *in vivo* potency and duration at least in part by inhibiting metabolism of the side chain.[22,23] The orientation of the amphetamines compared to tryptamines in binding to the 5-HT_2 receptor is still a matter of speculation, but the aspartic acid residue in TMD 3 is thought to bind to the protonated side chain amine, as with the tryptamines. A model of amphetamine binding proposed by Monte *et al.* is shown in Figure 8.

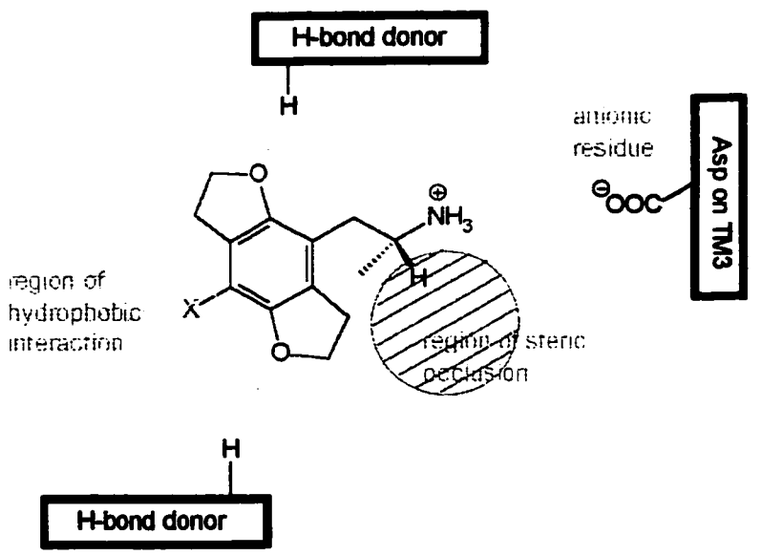


Figure 8. Monte's model of substituted amphetamine binding at the 5-HT_2 receptor.[23]

In addition to the 5-HT_{1A} and 5-HT_{2A} receptors, Sanders-Bush[24] has shown that hallucinogenic drugs have agonistic activity at 5-HT_{1C} receptors (now called 5-HT_{2C}). Their ability to cause phosphoinositide hydrolysis in general followed their potencies in humans as hallucinogens.

5-HT_{1A} Receptor

Investigation of the 5-HT_{1A} receptor was accelerated with the discovery of the selective agonist 8-hydroxy-2-(*N,N*-dipropylamino)-tetralin (8-OH-DPAT), shown in Figure 9.[25] This discovery ultimately allowed the development of selective 5-HT_{1A} agonists that have been used as novel anxiolytics (i.e. buspirone).

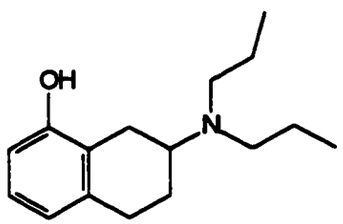


Figure 9. Selective agonist for the 5-HT_{1A} receptor, 8-OH-DPAT.

Kuipers and coworkers[26] carried out a study using bacteriorhodopsin as the structural template to build a model of the 5-HT_{1A} receptor. The 3-dimensional structure of bacteriorhodopsin has been solved, and although this protein is not G-protein coupled, mammalian rhodopsin is coupled to the G-protein transducin. Through mutation studies and molecular modeling of the binding pocket, the authors developed conclusions about

the agonist and antagonist binding sites. Asp^{116} in TMD 3 apparently binds to the protonated side chain amine. Ser^{199} and Thr^{200} (TMD 5) both appeared important in agonist binding. Neither of these residues affected the binding of the antagonist pindolol. A single point mutation of Asn^{386} in TMD VII performed by Peroutka *et al.*[27] decreased the affinity of aryloxyalkylamine antagonists, but did not effect the binding of serotonin or 8-OH-DPAT.

However, the agonist binding site proposed by Kuipers,[26] (see Figure 10) does not explain the high affinity of 8-OH-DPAT. The authors suggest the side chain *n*-propyls interact with hydrophobic residues in the area between TMD 3 and TMD 4 to regain the affinity lost due to the lack of an indole NH. Val^{117} and Cys^{120} are in this region, and are unique to the 5-HT_{1A} receptor. Also, the 5-HT_2 receptor has a Ser^{120} in place of Cys^{120}, possibly explaining the lower affinity of 8-OH-DPAT for the 5-HT_2 receptor. In their computer model the 6 and 7 positions of tryptamines are close to the backbone of helix 5, and the 2 position is close to the backbone of helix 4. Substitutions at these positions decrease the affinity of tryptamines at the 5-HT_{1A} receptor.[28]

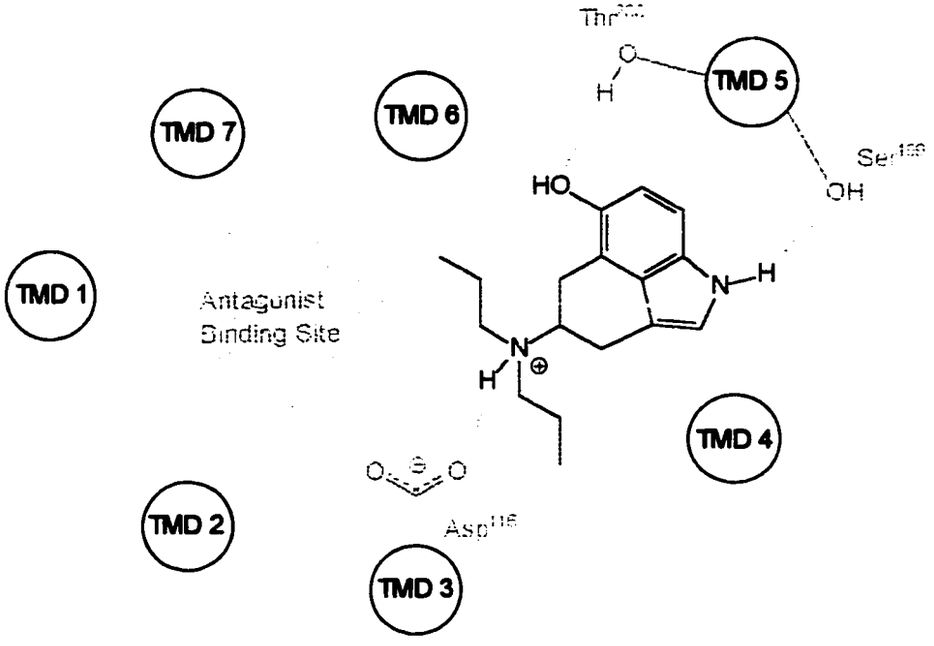


Figure 10. Kuipers proposed model of agonist binding at the 5-HT_{1A} receptor. [26]

Fluorine and Fluorinated Derivatives of Bioactive Compounds

Fluorine can dramatically change the biological profile of active compounds, and have an influence on the metabolism and distribution of drug molecules in the body. Substitution of fluorine at various positions of the aromatic ring of the neurotransmitter norepinephrine produces large differences in biological activity.[29] Fluorinated melatonin analogs have enhanced activity at the pituitary melatonin receptor, in addition to increased biological half-life.[30] Phenol acidity is significantly increased in fluorinated tyramine,

dopamine, and serotonin analogs.[31,32] Also, the *para*-fluorophenyl group is optimal for the neuroleptic activity of butyrophenones, such as haloperidol (Figure 11).[33]

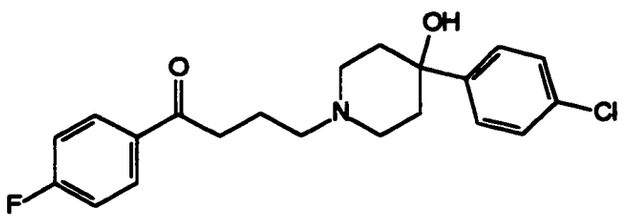


Figure 11. Haloperidol

The fluorine atom is nearly the same size as a hydrogen atom (Figure 12), but has very different electronic properties.[34] Fluorine is a stronger hydrogen bond acceptor than other halogens, but weaker than a hydroxyl. Fluorine could also mimic a hydroxyl through a dipole-dipole interaction. For instance, muscarine analogs in which fluorine replaced the hydroxyl in the 4-position, producing either equal or slightly increased affinity for the muscarinic M_2 receptor.[35] Fluorine substitution may affect the hydrogen bonding properties of phenols, in addition to the lability of phenols to be oxidized to quinones. Fluorine can also increase the lipophilicity of a molecule to allow better partitioning into membranes and facilitate hydrophobic interactions with a target receptor. This is particularly useful for CNS-active drugs that must cross the blood-brain barrier to reach their site of action. In addition, site-specific metabolic blockade can be achieved by fluorine substitution.

	van der Waals radius	bond energy of C-F or C-H	hydrophobic constant π	Hammett σ_p	Hammett σ_m
F	1.35 A	112 kcal/mole	0.13	0.15	0.34
H	1.20 A	98 kcal/mole	0.00	0.00	0.00

Figure 12. Properties of the fluorine and hydrogen atoms.

A series of analogs of 4-(4-hydroxyphenyl)butan-2-one, the principle flavoring component of raspberries, was tested for their ability to retain the parent compound's natural taste and smell.[36] The analogs that contained fluorine in various positions retain very similar properties, while methyl substitutions in the same positions produced compounds that had dramatic differences in taste and smell (see Figure 13). Fluorine, rather than a methyl group, was a much better replacement of hydrogen, at least with respect to the taste receptors and the sensory receptors in the nasal passages.

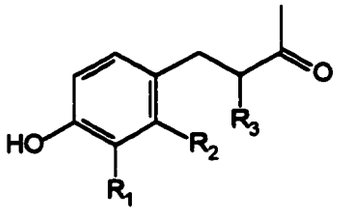


Figure 13. Analogs of the active flavoring component of raspberries (R_1=R_2=R_3=H). Individual replacement of R_1, R_2, or R_3 with fluorine resulted in molecules with similar sensory properties, while molecules with methyl replacement of the R groups displayed very different changes in their taste and smell.[36]

Ab initio calculations of hydrogen bonds of fluoromethane or fluoroethene with water resulted in the hydrogen bond values shown in Figure 14.[37] The geometries were optimized at the second order Möller-Plesset level utilizing analytical gradients as implemented in the GAMESS program (see reference 37). The basis set used was Dunning's TZV supplemented by 3d and 1f polarization functions with Bearpark and Handy's "V" exponents and also a diffuse sp shell for C, O, and F (see reference 37). However, these hydrogen-bonding interactions would never be seen in water, and are only calculated for the isolated molecules.

Other theoretical calculations estimate the strength of the intramolecular F···H bond in 2-fluoroacetaldehyde enols to be as high as 3.53 kcal/mole (see Figure 14).[38] In spite of the fact that the F···H bond is weaker than a hydrogen bond with oxygen at 5-10 kcal/mole,[37] it should be kept in mind that within the constraints of a hydrophobic receptor pocket, a F···H bond may be favored in some situations compared to an oxygen or a hydroxy group. Indeed, the fluorine substituent must be isolated from an aqueous environment (such is the case in a receptor pocket) in order to be involved in a hydrogen-bonding interaction.

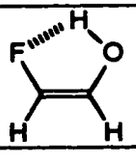
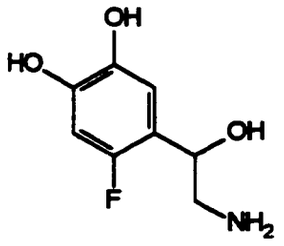
O····H	$C(sp^3)$—F····H_2O (fluoromethane)	$C(sp^2)$—F····H_2O (fluoroethene)	
5-10 kcal/mole	2.38 kcal/mole	1.48 kcal/mole	3.53 kcal/mole

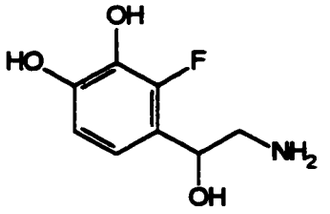
Figure 14. Energy values of oxygen and fluorine hydrogen bonds.[37,38]

The fluorine atom may also have an effect on nearby functional groups due to repulsive forces. Fluorinated norepinephrine analogs were either α- or β-adrenergic agonists, depending on the location of the fluorine (see Figure 15a).[39,40] Fluorine seems to cause a preferred side chain orientation by an electrostatic repulsion of a benzylic hydroxyl. Data from a series of cyclized α-adrenergic catechol compounds supported this fluorine-OH electrostatic repulsion theory (Figure 15b).[41] The rigid analogs that had structures similar to the theoretical conformations of the fluoro-norepinephrines had parallel affinities for α-adrenergic receptors. Fluorine also produced α- or β-selectivity in ring-fluorinated phenylephrine compounds.[42]

(a)



selective α-agonist



selective β-agonist

Figure 15. The relative α-receptor affinities of a series of fluorinated norepinephrine analogs and cyclized α-adrenergic compounds are consistent with the fluorine-hydroxyl electrostatic repulsion theory.[39-41]

Fluorine can possess dual properties in aromatic substitution reactions (electron donating properties/inductive electron withdrawing effect). In addition, fluorine can possess counteracting attractive and repulsive forces (hydrogen bonding/electrostatic repulsive forces) which may affect the affinity of a fluorinated ligand, depending on the nature of the molecule and the molecular recognition properties of the particular receptor binding pocket.

Fluorinated Hallucinogenic Tryptamines

Szara *et al.*[43] in 1963 published a report that 6-F-DET (6-fluoro-*N*,*N*-diethyltryptamine) was inactive as a hallucinogen (Figure 16). Although autonomic symptoms similar to the parent compound DET were observed, along with some mood changes, 6-F-DET did not produce the perceptual and visual disturbances characteristic of

hallucinogens. This complete loss of activity indicated some unknown effect on the mechanism of action of this hallucinogen, possibly producing a change in affinity, efficacy, and/or selectivity at the serotonin receptor subtypes.

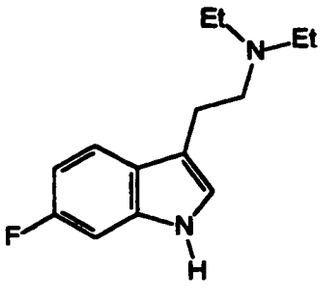
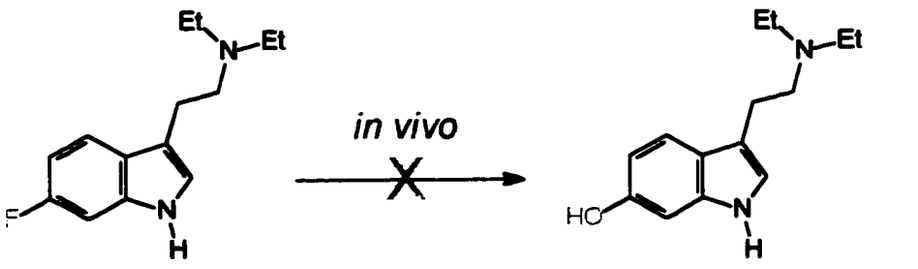


Figure 16. 6-F-DET produced autonomic symptoms, but lacked hallucinogenic activity.

Although Szara originally attributed this to inhibition of the metabolism of DET to an "active" metabolite, 6-hydroxy-DET, the idea was not proven (see Figure 17). In fact, a report seven years earlier had indicated that 6-hydroxy-DMT was devoid of hallucinogenic activity.[44] DET would have similar metabolic pathways, and activities of the metabolites should also be similar, considering the only change in structure is the alkyl groups on the side chain amine. Although lacking hallucinogenic activity, 6-F-DET proved to be useful as an "active placebo" in clinical trials, due to its activation of the autonomic nervous system[45]



inactive hallucinogen postulated "active" hallucinogen

Figure 17. Hypothesis to explain the lack of hallucinogenic activity of 6-F-DET.[43]

The question naturally arose: does ring-fluorination inactivate other potent hallucinogens such as psilocin and 5-methoxy-DMT? What change in molecular recognition is taking place at serotonin receptors? Such questions had never been addressed. Currently, selective ligands are available that were not available 25 years ago, to determine the binding profile of a compound at several serotonin receptors, most importantly the 5-HT_{1A} and 5-HT_{2A} receptors. Therefore, the binding profile of 6-F-DET can now be determined.

Since the 3-dimensional structures of serotonin receptors are not available, compounds with altered affinity and selectivity can provide valuable information about the topography of the binding sites, and aid in the design of derivatives with higher affinity and selectivity.

Thienopyrrole Analogs as Bioisosteres of Tryptamines

Bioisosteres are isosteric molecules that have similar or antagonistic properties in biological systems. Previously, benzo[*b*]thiophenes have been examined as bioisosteres of indoles in several types of biologically active molecules. For example, the benzo[*b*]thiophene analogue of DMT was prepared and evaluated *in vitro* many years ago (Figure 18). While it had *in vitro* pharmacology similar to that of DMT, its behavioral effects in rabbits differed.[45] The benzo[*b*]thiophene analogue of psilocin (Figure 18) was prepared by Campaigne and coworkers and its pharmacology also differed somewhat from that of psilocin.[47] In a similar vein, the benzo[*b*]thiophene analogue of 5,6-dihydroxytryptamine, a serotonin neurotoxin, failed to affect serotonin levels but did cause depletion of norepinephrine.[47]

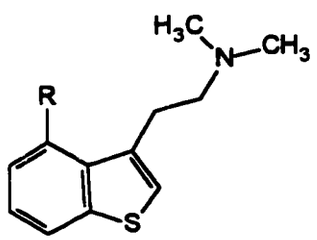


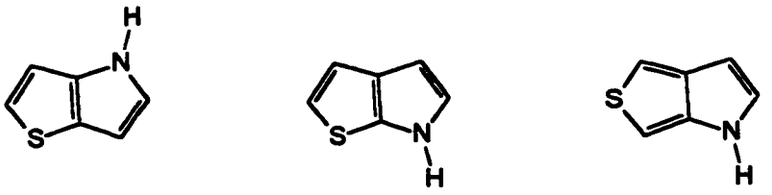
Figure 18. Benzo[*b*]thiophene analogs of DMT (R=H) and psilocin (R=OH).

On the other hand, thiophene replacement of the annulated benzene ring in derivatives of piroxicam, an antiinflammatory agent used in arthritis patients, had no significant effect on activity.[48] Similarly, the thiophene analogue of amphetamine retains

complete amphetamine-like activity.[49] In addition, replacement of the phenyl ring with a thienyl ring in dopaminergic phenyl-tetrahydro-isoquinolines and benzo[*a*]phenanthridines led to compounds with biological activity virtually identical to their phenyl counterparts.[50]

Thus, it is clear that replacing the nitrogen atom in the indole with sulfur (or oxygen)[51] gives compounds that do not predictably retain biological properties analogous to their indole counterparts. On the other hand, replacement of the phenyl ring of indole with a thiophene, which leads to thienylpyrroles, appeared more likely to result in bioisosteres with comparable biological properties. However, because the resonance stabilization energy for thienopyrrole is less than that for indole, charge-transfer or face-to-edge aromatic ring stacking interactions involved in molecular recognition at serotonin receptors may be affected.

Molecular orbital calculations indicate that the stabilities of the thienopyrrole isomers differ significantly.[52,53] Annulation at 2,3 bonds (Figure 19a and 19b) produced more stable thienopyrroles than annulation at the 3,4 bond of thiophene and a 2,3 bond of pyrrole (Figure 19c). Annulation at both 3,4 bonds gave compounds that proved to be highly unstable.



(a) (b) (c)

Figure 19. Thieno[3,2-*b*]pyrrole (a), thieno[2,3-*b*]pyrrole (b), and thieno[3,4-*b*]pyrrole (c).

The compounds in Figure 19 (a and b) themselves are air-sensitive at room temperature.[52] Recently, two of the three possible thienopyrrole analogues of tryptophan were synthesized.[54] The synthesis of the third isomer, having thieno[3,4-*b*]pyrrole (Figure 19c) as the nucleus, was not completed due to the instability of this positional isomer. The *N*-BOC-protected aryl acetic acid ethyl esters representing all three nuclei shown in Figure 19 were also previously prepared, but deprotection of the respective derivative of thieno[3,4-*b*]pyrrole led to decomposition.[55]

Taking into account the theoretical and experimental stability considerations, it would be difficult, if not impossible, to isolate a tryptamine analog containing the unstable thieno[3,4-*b*]pyrrole nucleus. Therefore, 6-[2-(*N*,*N*-dimethylamino)ethyl]-4*H*-thieno[3,2-*b*]pyrrole and 4-[2-(*N*,*N*-dimethylamino)ethyl]-6*H*-thieno[2,3-*b*]pyrrole (Figure 20a and 20b, respectively), would be accessible and interesting entries into the investigation of thienopyrrole positional isomers of DMT.

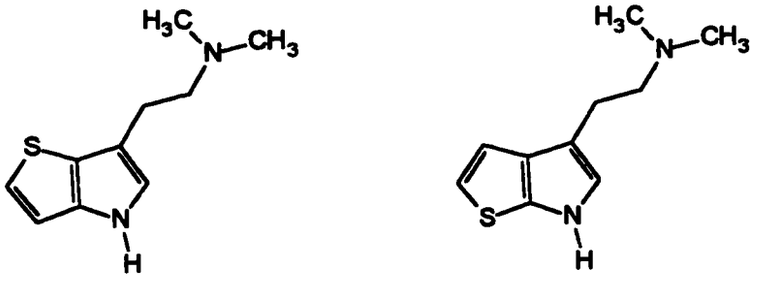


Figure 20. Thienopyrrole positional isomers of DMT.

RATIONALE

The serotonin receptor system is a challenging target for synthetic medicinal chemists attempting to define the molecular recognition requirements and structure activity relationships of selective ligands. The inherently unlikely event in which a small molecule diffuses into and binds with a receptor pocket occurs because a molecule's electronic and steric properties are optimized for recognition at a particular receptor.

In the case of serotonin receptors, subtle differences can change the characteristics of a molecule to increase affinity for one receptor subtype over another. Several serotonin receptor ligands have high affinity but are nonselective (i.e. 5-methoxy-DMT, LSD), usually limiting medicinal potential. Optimization of low affinity compounds via analogs with increased binding is one approach to define molecular recognition. However, another approach is to synthesize analogs of high affinity compounds to not only further improve affinity, but also to strive to produce selectivity for serotonin receptor subtypes. In many cases, SAR becomes a "hit and miss" situation where some educated guessing is involved in the design of future derivatives. The SAR of previous compounds provides information about the structural and electronic properties required, and future analogs incorporate modifications based on this information.

The dramatic change in biological effects produced by fluorination of DET (discussed earlier in the introduction) was taken as a possible lead for new derivatives. The sometimes contradicting electronic properties of fluorine, along with a 3-dimensional receptor pocket that is largely unknown, makes evaluation of SAR at serotonin receptors

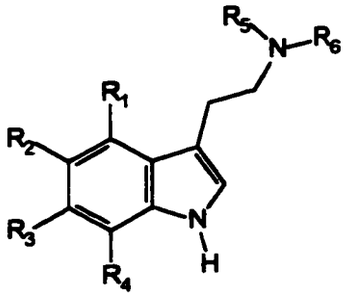
difficult. Nevertheless, the ultimate goal is the development of high affinity compounds with selectivity for one receptor subtype. Selective ligands can be used as molecular probes to determine the specific function(s) of the receptor subtype, along with the development of high affinity radioligands to screen future compounds more selectively. The need for antagonists to block secondary receptors in receptor binding assays is eliminated. Another benefit is reducing unwanted or undesirable side effects produced by interaction with secondary receptors that can reduce the medicinal potential and obscure behavioral results.

With these considerations in mind, 5-methoxy-DMT, psilocin, and DMT (or DET) seemed logical starting points in the search for selective ligands based on hallucinogenic tryptamines. The affinities of these three compounds are shown in Table 2, with binding at the 5-HT_{1A} receptor defined by the ability to displace [^{3}H]8-OH-DPAT in rat cortex tissue and at the 5-HT_{2A} receptor by the ability to displace [^{125}I]DOI in rat cortex.[17] Unlike 5-methoxy-DMT and DMT, psilocin has a 30-fold selectivity for the 5-HT_{2A} receptor.

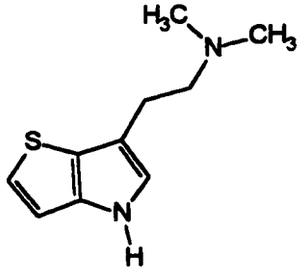
Table 2. Inhibition constants for hallucinogenic tryptamines.[17]

	IC_{50}[nM]	
Compound	5-HT_{1A}	5-HT_{2A}
5-Methoxy-DMT	6.5 ± 1.5	14 ± 1
Psilocin	190 ± 40	6.0 ± 0.5
DMT	170 ± 35	75 ± 16

Fluorinated derivatives synthesized in this work are shown in Figure 21. The fluorinated compound (**1**) along with 6-fluoro-DMT (**2**) was resynthesized and compared to the other analogs in biological testing. Additional fluorinated and difluorinated analogs include 4-fluoro-DMT (**3**), 5-fluoro-DMT (**4**), 4,5-difluoro-DMT (**5**), 5,6-difluoro-DMT (**6**), and 4,7-difluoro-DMT (**7**). Fluorinated derivatives of the potent hallucinogens psilocin and 5-methoxy-DMT were also prepared, including 6-F-psilocin (**8**), 7-fluoro-psilocin (**9**), 6-flouro-5-methoxy-DMT (**10**), and 4-fluoro-5-methoxy-DMT (**11**). The two thienopyrrole bioisosteres of DMT (**12** and **13**) were prepared to evaluate the validity of replacing the indole nucleus with a thienopyrrole moiety.



R_1	R_2	R_3	R_4	R_5=R_6	Compound	Name
H	H	F	H	CH_2CH_3	1	6-fluoro-DET
H	H	F	H	CH_3	2	6-fluoro-DMT
F	H	H	H	CH_3	3	4-fluoro-DMT
H	F	H	H	CH_3	4	5-fluoro-DMT
F	F	H	H	CH_3	5	4,5-difluoro-DMT
H	F	F	H	CH_3	6	5,6-difluoro-DMT
F	H	H	F	CH_3	7	4,7-difluoro-DMT
OH	H	F	H	CH_3	8	6-fluoro-psilocin
OH	H	H	F	CH_3	9	7-fluoro-psilocin
H	OCH_3	F	H	CH_3	10	6-flouro-5-methoxy-DMT
F	OCH_3	H	H	CH_3	11	4-fluoro-5-methoxy-DMT



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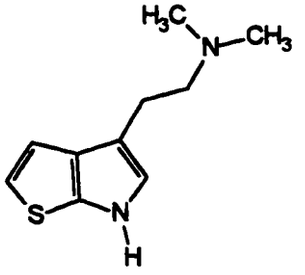

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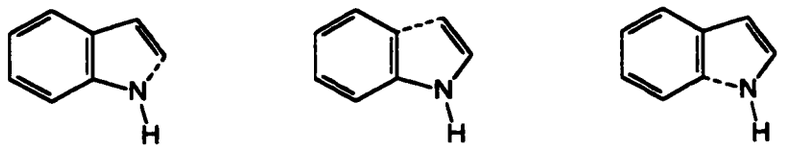
Figure 21. Target Compounds.

RESULTS AND DISCUSSION

Synthesis

Most indole formation reactions start with functionalized arenes which are then cyclized to the indole nucleus. Recent developments in indole ring syntheses have been reviewed.[56] The final bond-formation process most commonly occurs at three locations, indicated by dashed lines in Figure 22.[57]



a. b. c.

Figure 22. Indole synthesis: Final bond formation.

The most extensively developed indolization process is formation of the N(1)-C(2) bond (Figure 22a). This includes the Leimgruber-Batcho method, based on the condensation of *o*-nitrotoluene with *N,N*-dimethylformamide dimethylacetal followed by reduction of the resulting *trans*-β-dimethylamino-2-nitrostyrene (Figure 23),[58] and also the Reissert synthesis which involves the base-catalyzed condensation of an *o*-nitrotoluene with an oxalate ester followed by reductive cyclization (Figure 24).[59]

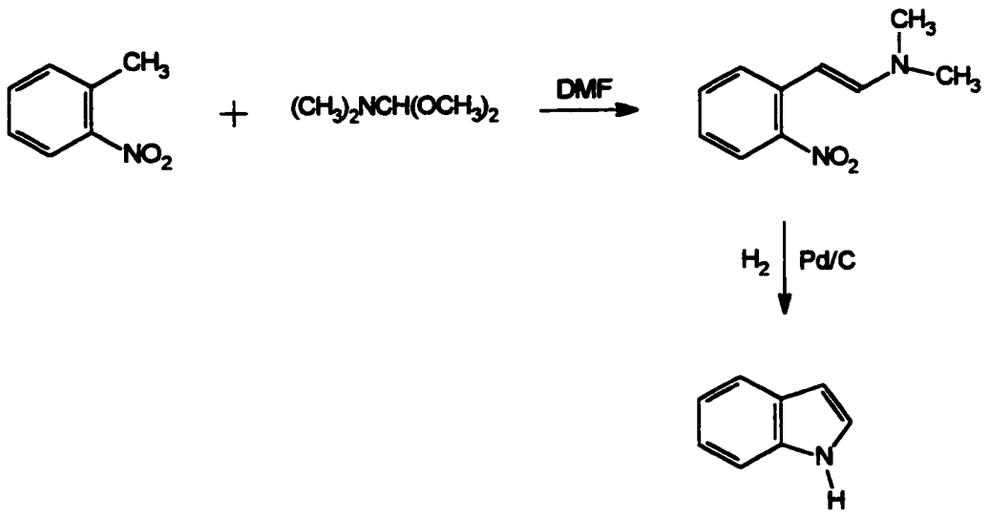


Figure 23. Leimgruber-Batcho indole synthesis.

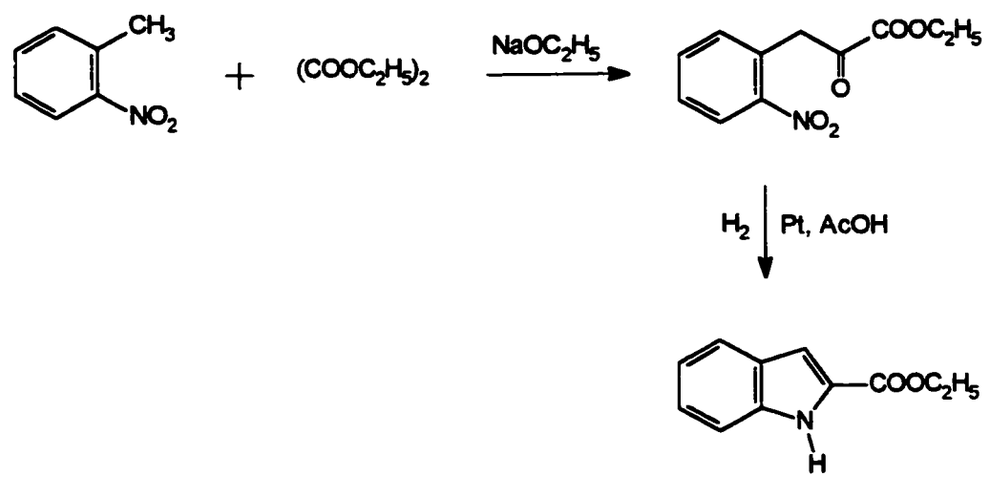


Figure 24. Reissert indole synthesis.

The classic Fischer indole synthesis is an example of indolization by bond formation at C(3)-C(3a) (Figure 22b). This method involves the cyclization of arylhydrazones usually under acidic conditions, or with a metal catalyst, with the loss of ammonia (Figure 25). The Fischer indole synthesis and its mechanism have been reviewed.[60,61]

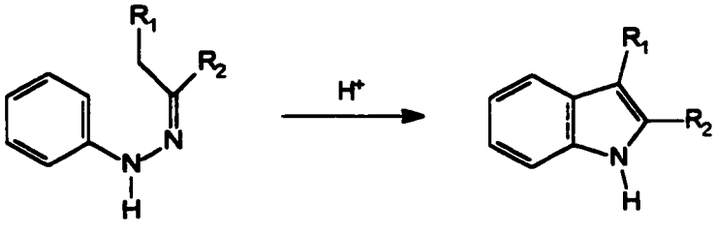


Figure 25. The Fischer indole synthesis.

Indole cyclization procedures (such as the Fischer method) frequently give 5-, 6- or 7-substituted products. A particularly attractive method to obtain 4-substituted indoles or otherwise fix the resulting indole substitution pattern, is the Hemetsberger Reaction[62,63] developed about 1969-70 but later popularized by Moody *et al.*[64,65] and sometimes called the "Moody azide pyrolysis."[64-68] Aromatic aldehydes are condensed with ethyl azidoacetate under basic conditions, followed by ring closure in refluxing toluene or xylenes (Figure 26). The azidocinnamate method effects ring closure by bond formation at C(7a)-N(1) (Figure 22c).

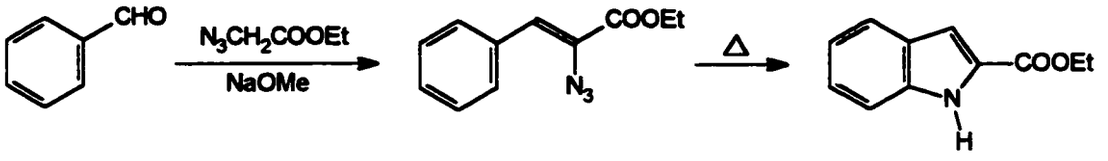
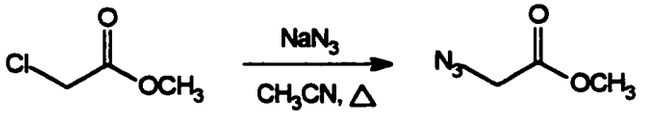


Figure 26. Hemetsberger method of indole synthesis.[62,63]

Fluorinated Tryptamines

Derivatives **1**, **2**, **8**, and **9** were prepared via the Hemetsberger Reaction. 6-F-DET (**1**) and 6-F-DMT (**2**) have been previously made by different methods.[43,69] Methyl azidoacetate (**15**) was prepared by treating methyl chloroacetate with sodium azide following literature procedures (Figure 27).[66]



14 **15**

Figure 27. Synthesis of methyl azidoacetate.[66]

The syntheses of **1** and **2** (Figure 21) have as a common intermediate: the glyoxyl chloride **21** (Figure 28). The azidocinnamate **17** was formed from *p*-fluorobenzaldehyde and **15**, followed by thermal cyclization to give the carboxymethylindole **18**, according to literature methodology.[66,68] The ester was hydrolyzed, followed by decarboxylation at high temperature in excellent yields. The decarboxylation method was improved in our laboratory using *N*-methylpyrrolidinone as the solvent rather than quinoline, which has the advantage of the easy removal of *N*-methylpyrrolidinone in the workup as opposed to the difficulty in removing quinoline. In addition, the decarboxylation was performed with a stream of nitrogen constantly bubbling through the refluxing solution presumably to remove carbon dioxide. Up to 15% increases in yields were obtained by this decarboxylation method in the syntheses of compounds **1**, **2**, **8**, and **9**. The glyoxylamides **22** and **23** were prepared by acylation of **20** with oxalyl chloride followed by treatment with diethyl- or dimethylamine, according to the method of Speeter and Anthony.[70] Reduction of **22** and **23** with LAH then afforded **1** and **2**, respectively.

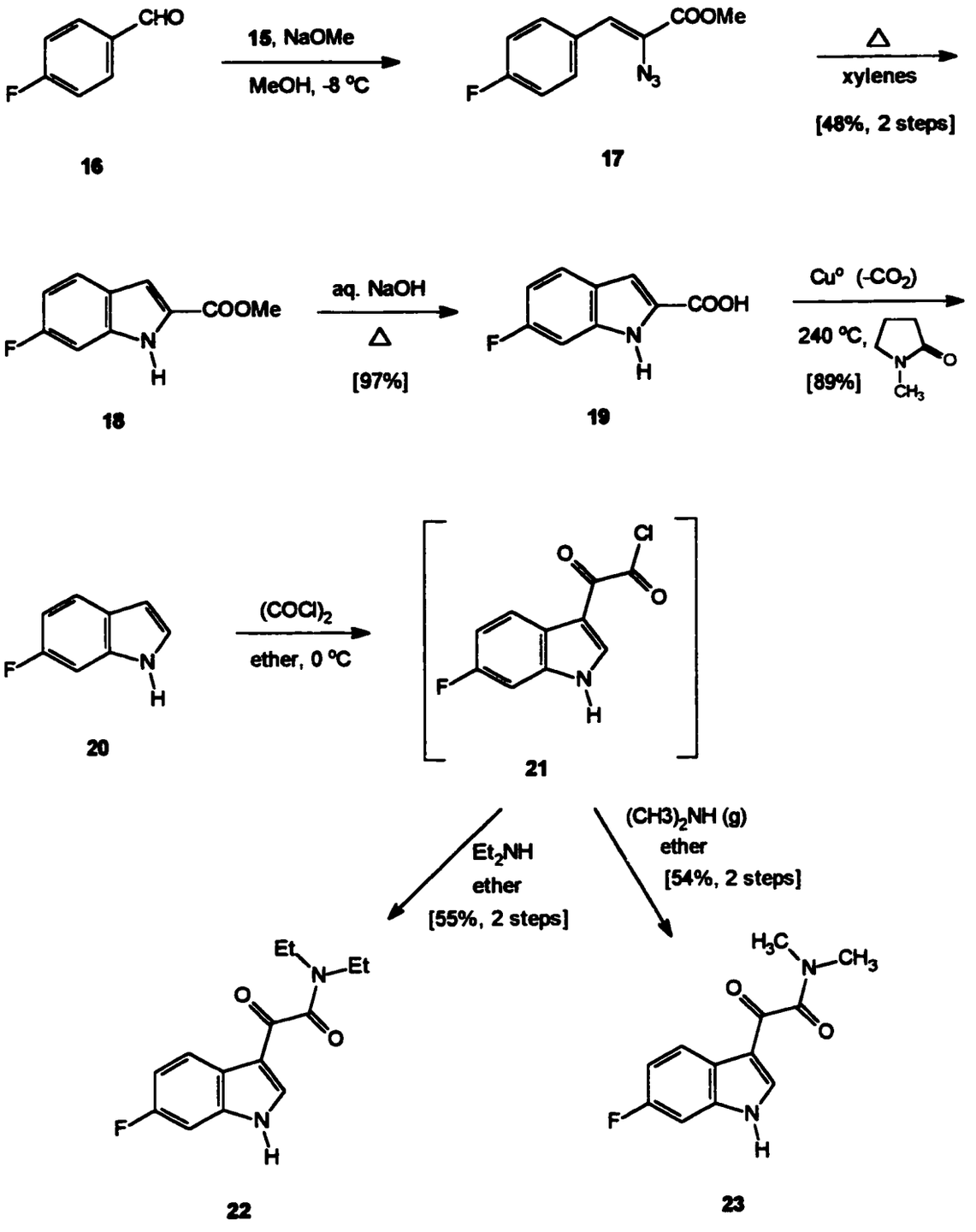


Figure 28. Synthesis of 6-fluorotryptamines 1 and 2.

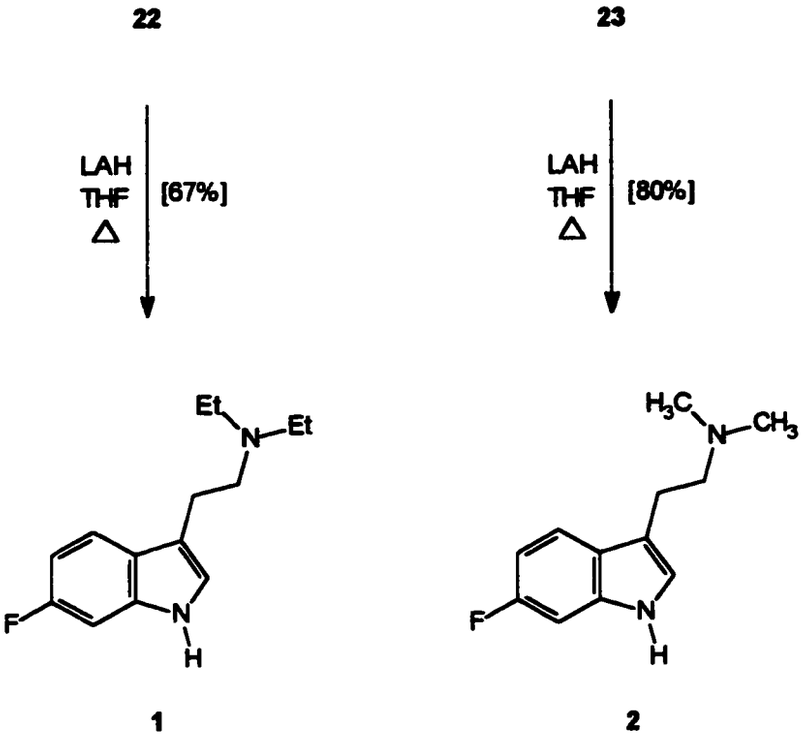


Figure 28, continued.

The 6-fluoro and 7-fluoro analogs of psilocin, **8** and **9**, were also prepared using the Hemetsberger reaction (Figures 29 and 30). 6-Fluoropsilocin had been a target in our laboratory for many years, but was not readily accessible by previously known indole synthetic methods until the development of the Hemetsberger reaction. Since the starting *ortho*-formylated phenol is required for the final 4-hydroxy tryptamine, the first step in the syntheses of **8** and **9** involved an *ortho*-specific formylation of *meta*-fluorophenol. Formylation of free phenols frequently results in low yields, poor regioselectivity, and/or *para*-formylation as the major result. In addition, formylations using metal catalysts generally require high pressure. Aldred *et al.*[71] recently reported the successful *ortho*-

formylation of magnesium bis(phenoxides), prepared from phenols and magnesium methoxide, using paraformaldehyde and methanol as the cosolvent instead of the toxic hexamethylphosphoramide.

Starting phenols **24** and **34** were therefore formylated to yield the salicyladehydes **25** and **35**. Protection of the phenol functionalities with a benzyl group, followed by condensation with methyl azidoacetate resulted in the azidocinnamates **27** and **37**, which cyclized in refluxing xylenes to yield the carboxymethyl indoles **28** and **38**. Cleavage of the esters, followed by decarboxylation, and elaboration of the side chains as discussed previously for the synthesis of **1** and **2**, yielded **33** and **43**. Removal of the benzyl protecting group by catalytic hydrogenation afforded the target compounds **8** and **9**.

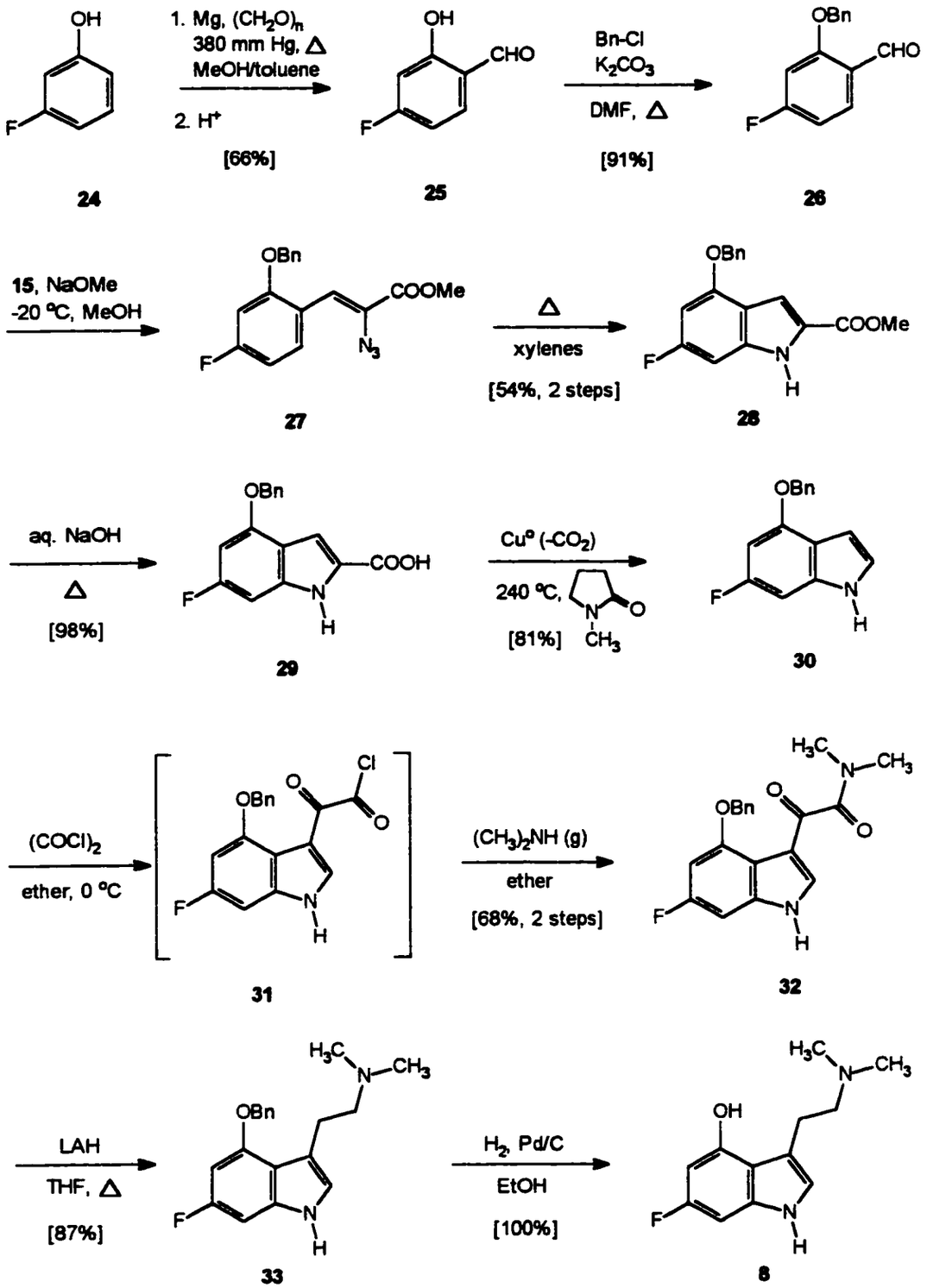


Figure 29. Synthesis of 6-fluoropsilocin.

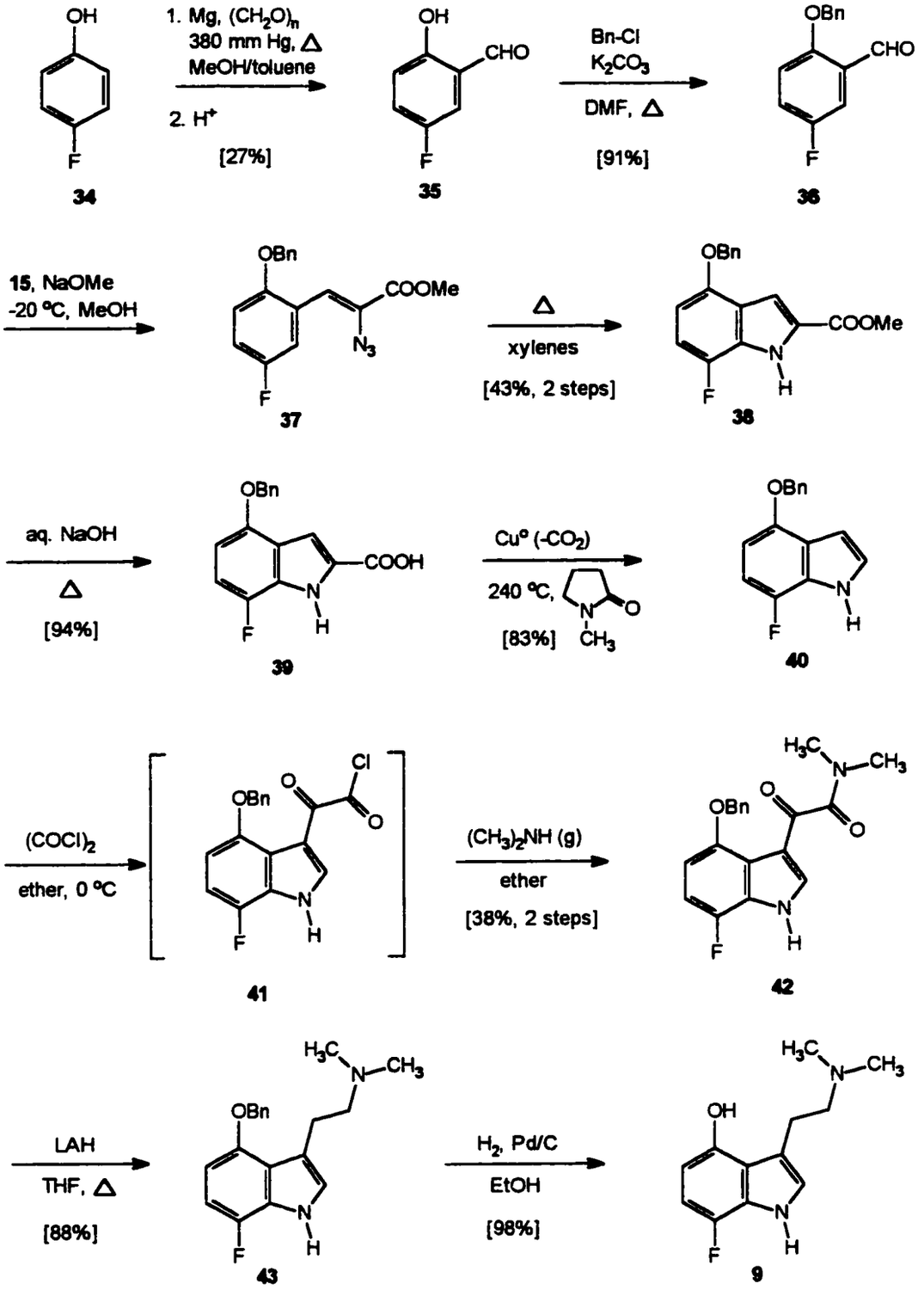


Figure 30. Synthesis of 7-fluoropsilocin.

The remaining fluorinated derivatives (**3-7, 10, 11**) were prepared via Fischer indole cyclizations. The required acetal **47** was prepared according a literature procedure[72] as shown in Figure 31.

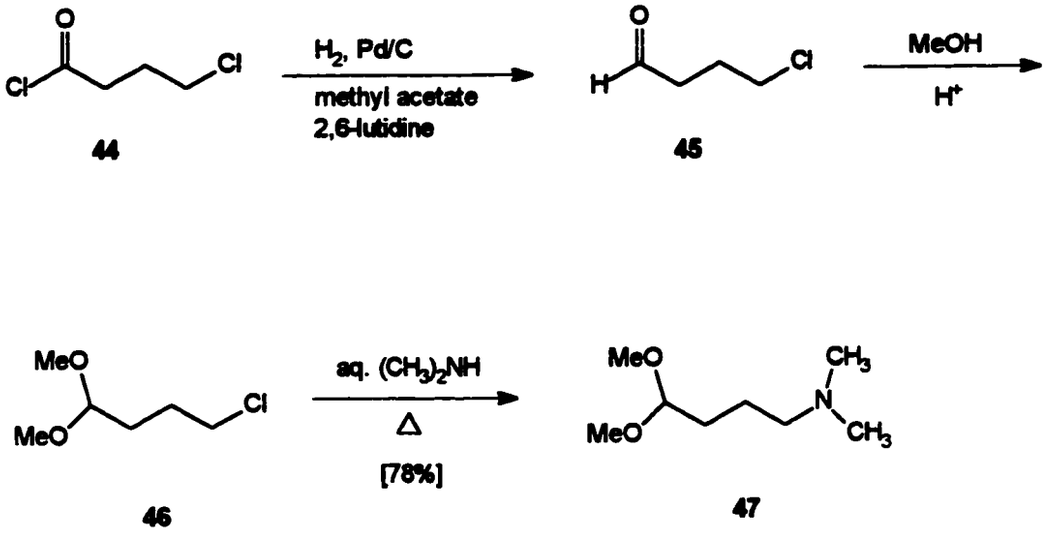


Figure 31. Synthesis of 4-(*N,N*-dimethylamino)-butanal dimethylacetal (**47**).[72]

Figure 32 outlines the synthesis of **10** and **11**, 6- and 4-fluorinated analogs of 5-methoxy-DMT. *Ortho*-fluoroaniline was converted to *ortho*-fluorophenol via the diazonium ion, following a similar procedure for 4-fluoro-3-hydroxytoluene by Claudi *et al.*[73] The phenol was then methylated followed by nitration to yield predominantly the *para*-nitroanisole **51**. Zeegers *et al.*[74] describe the nitration of anisole using catalytic amounts of $NaNO_2$ as a source of NO^+, and to also affect the *ortho/para* ratio of the products. It was implied that the increase in *para*-nitration was due at least in part to

oxidation of the intermediate nitroso compound. Also, Schofield *et al.*[75] earlier found that nitration of anisole in 65% H_2SO_4 in the presence of 0.04 M $NaNO_2$ led to a dramatic shift in the proportions of isomers, resulting in 94% *para*- and 6% *ortho*-nitroanisole. Thus, the intermediate **50** was nitrated under Schofields conditions but lower yields or amounts of *para*-nitrated products were formed. However, nitration of **50** in 66% H_2SO_4 with one equivalent of $NaNO_2$ and catalytic HNO_3 resulted in 60% yield of the *para*-nitrated product **51**. The *ortho*-isomer **52** could be detected in the ^{1}H-NMR spectrum, which indicated a yield of less than 1% for this isomer.

Anisidine **53** was prepared by catalytic reduction of **51**, followed by diazotization of the aniline and subsequent reduction with stannous chloride to yield the hydrazine **55**, by modifying the procedure of Street *et al.*[76] In 1964, Desaty *et al.*[77] reported formation of 5-methoxy-DMT in 74% yield in one step from *para*-methoxyphenyhydrazine hydrochloride in 25% acetic acid at 80^{O} C. Here, the fluorinated hydrazine **55** was treated with **47** to produce a 56% overall yield with the 6-fluoro isomer **10** as the major product.

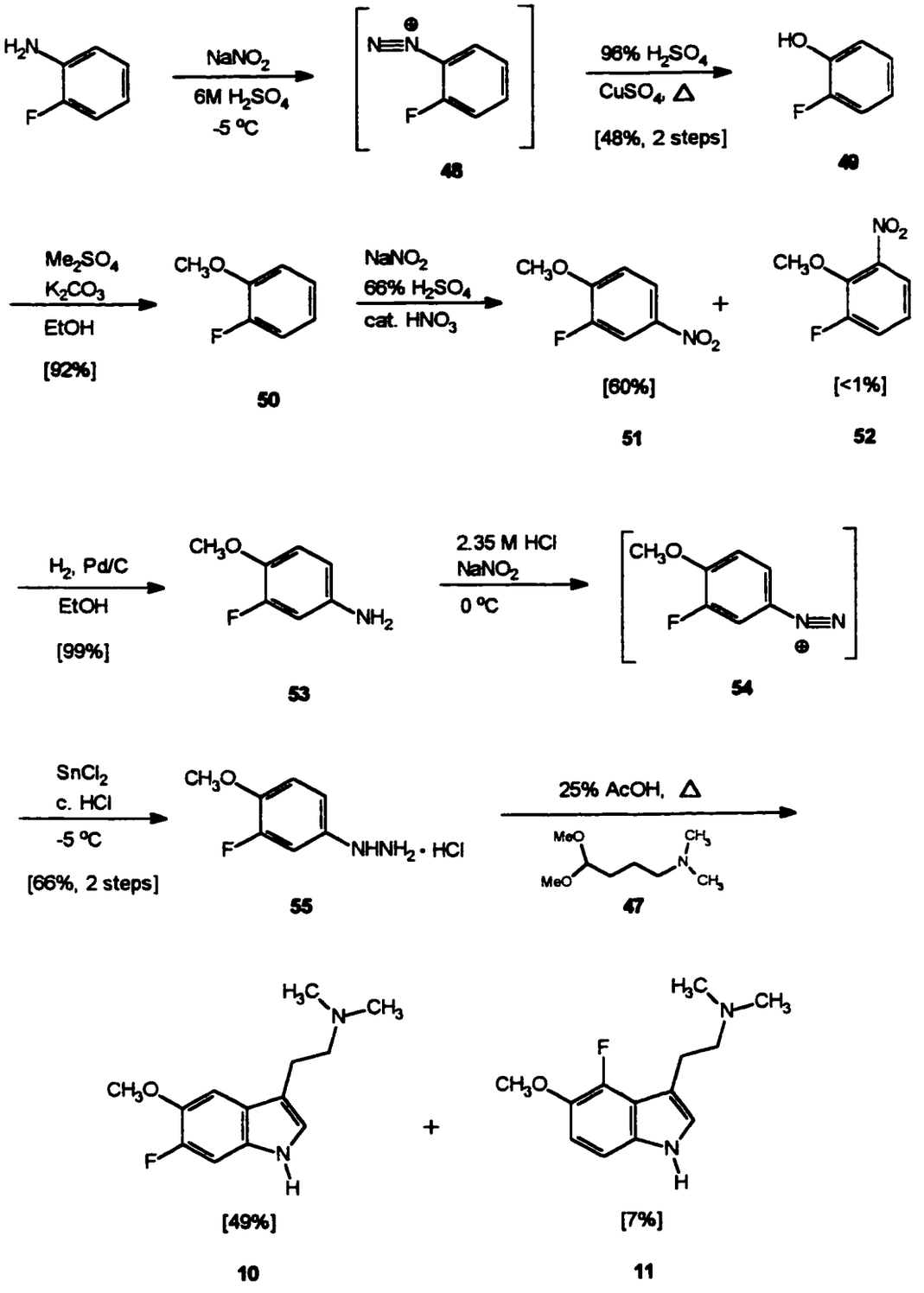


Figure 32. Synthesis of fluorinated analogs of 5-methoxy-DMT.

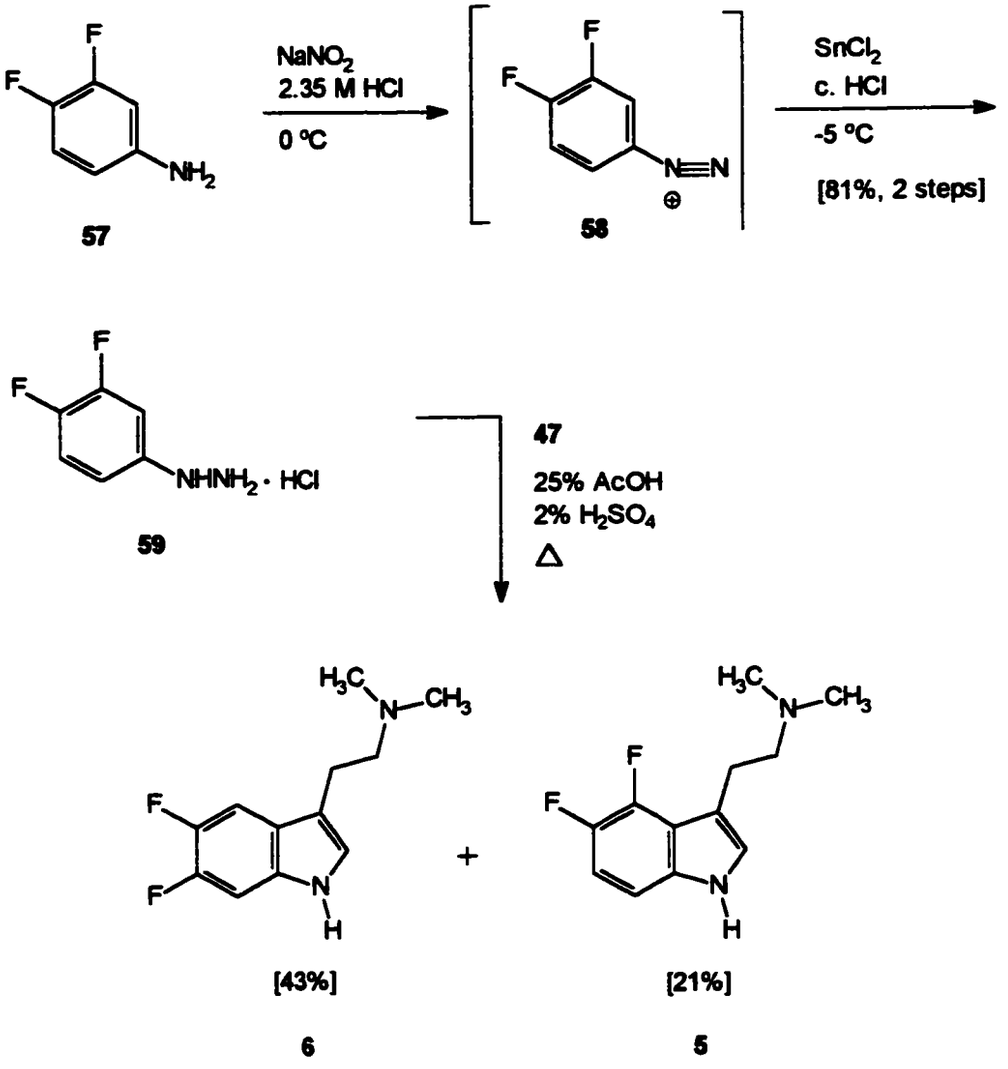


Figure 33. Synthesis of difluorinated tryptamines **5** and **6**.

Analogous reaction leading to the difluorinated tryptamines **5** and **6** occurred only sluggishly in 25% acetic acid. After 45 h, greater than 50% of the starting material remained. It was necessary to add the more strongly protonating sulphuric acid to

catalyze the Fischer cyclization (Figure 33). In this case, the reaction was complete in 22 h. The phenylhydrazine **59** was prepared following a procedure analogous to that of **55**, followed by cyclization in 25% AcOH/2% H_2SO_4 to give **5** and **6**, which were separated chromatographically.

4-Fluoro-DMT (**3**) and 5-fluoro-DMT (**4**) have been previously reported.[78,72] Fischer cyclization in 4% H_2SO_4 has been used to obtain indole derivatives[79] and was recently optimized using the acetal **47** for direct cyclization to *N,N*-dimethyltryptamines.[72] Therefore, *meta*-fluorophenylhydrazine hydrochloride (**56**) and **47** were treated with 4% H_2SO_4 (Figure 34) to give **2** (also prepared earlier using the Hemetsberger reaction) and the desired 4-fluoro-DMT (**3**), which were separated chromatographically. In spite of the fact that **3** was the minor product obtained, this was an efficient method to obtain a sample of this compound for testing without having to use the more involved Hemetsberger methodology. In a similar manner, **60** and **61** afforded 5-fluoro-DMT (**4**) and 4,7-difluoro-DMT (**7**) (Figure 34). The latter tryptamine was obtained as a dark oil that required several recrystallizations to obtain a 15% yield of pure crystals.

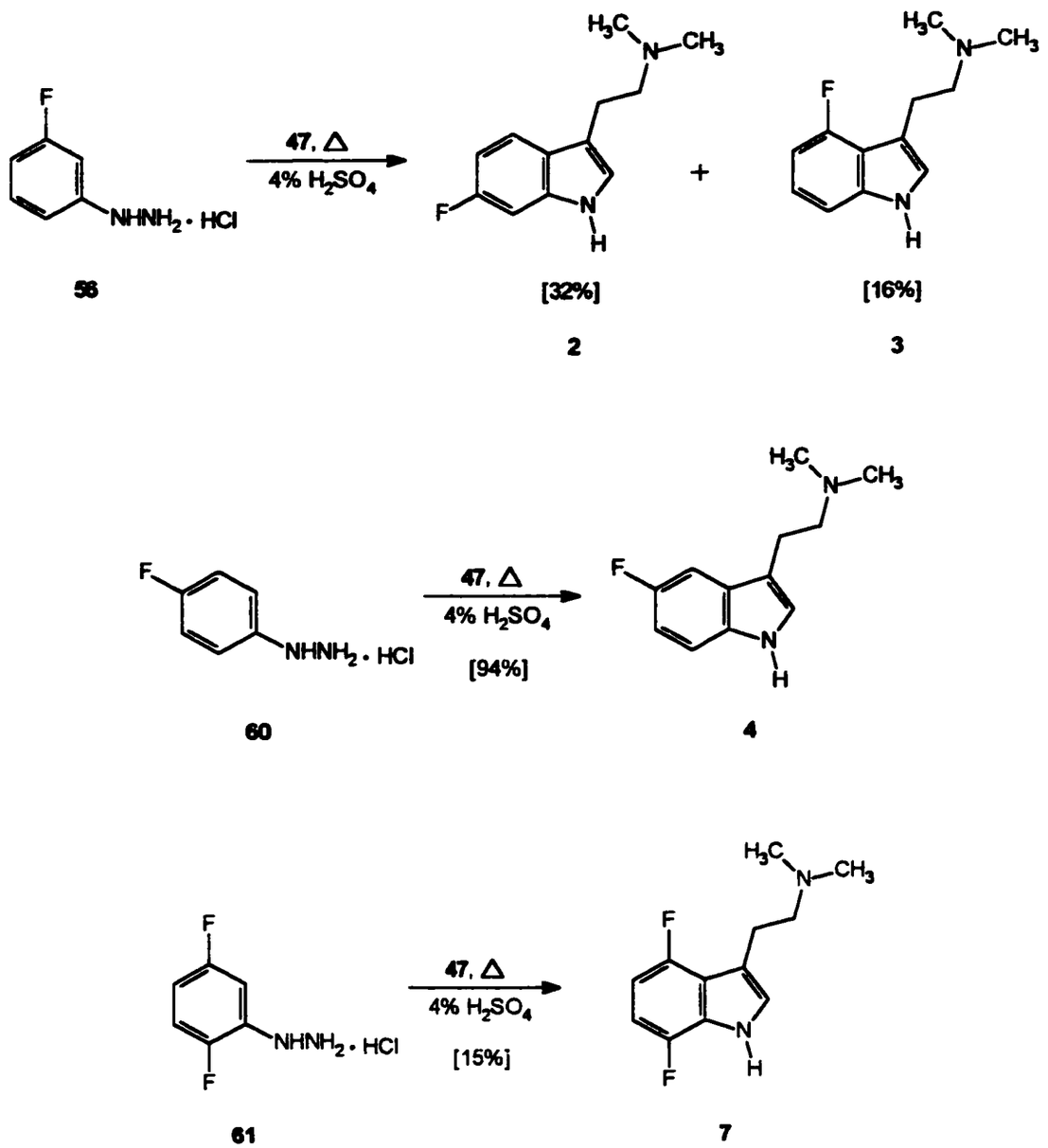


Figure 34. Fischer indole cyclizations in 4% H_2SO_4.

Thienopyrroles

Thienopyrroles consist of a pyrrole ring annulated with a thiophene ring and are of pharmacological interest since they are bioisosteric with indoles.[80] Several isomers of substituted thienopyrroles have been reported,[80-83] and a good review on the synthesis of thienopyrroles was published by Garcia *et al.*[80] Early attempts in this laboratory to prepare **12** and **13** were based on Fischer cyclizations to yield thienopyrrole derivatives reported in the literature[84-87] with electron withdrawing groups in the 2- or 5-position of the resulting thienopyrrole nucleus. Thiophene-2-carboxylic acid was converted to the BOC-protected 2-aminothiophene **67** under Curtius conditions,[88] followed by electrophilic amination with *O*-diphenylphosphinylhydroxylamine[89-94] (**64**), which is the first use of this electrophilic aminating reagent on an aminothiophene (Figure 35).

Alternative electrophilic aminating reagents such as *O*-2,4-dinitrophenyl hydroxylamine[95] and *O*-(4-nitrobenzoyl)hydroxylamine,[96] have been utilized in reactions with both carbon and nitrogen nucleophiles, but their preparation is laborious, expensive, and includes potentially explosive intermediate carbamates. Thus, deprotonation of **67** with sodium hydride followed by treatment with **64** yielded the BOC-protected thienylhydrazine **68** in excellent yield. Synthesis of the aminating reagent **64** is outlined in Figure 36. Treatment of chlorodiphenyphosphine with oxygen resulted in diphenylphosphinyl chloride (**63**),[97] and subsequent treatment with hydroxylamine hydrochloride and NaOH yielded **64**.[98]

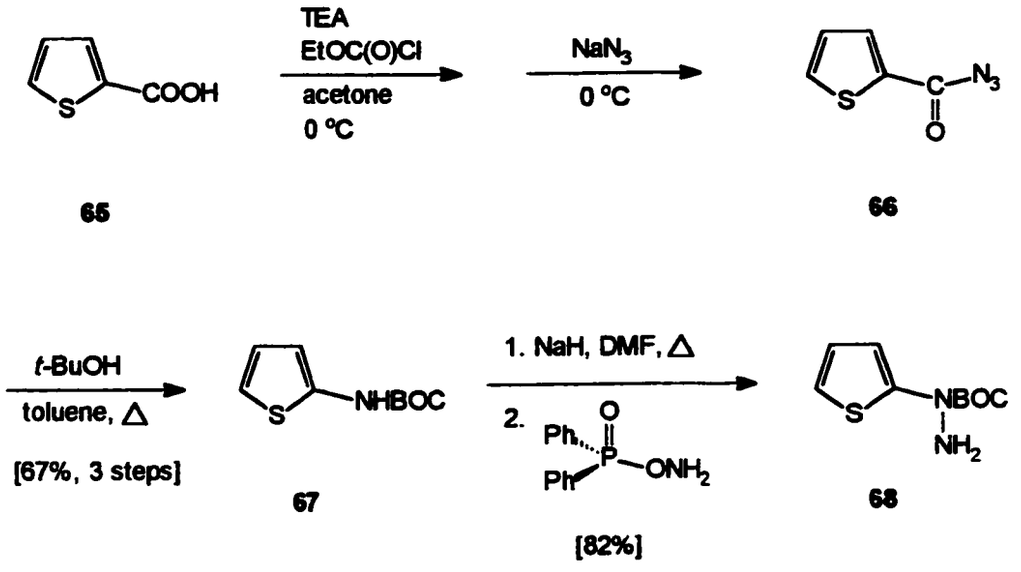


Figure 35. Synthesis of *N*-*t*-butoxycarbonyl-*N*-(2-thienyl)-hydrazine (**68**).

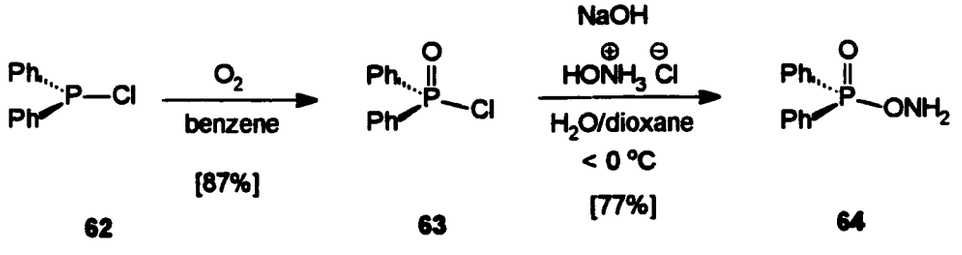


Figure 36. Synthesis of *O*-diphenylphosphinylhydroxylamine (**64**).

Attempted Fischer indole cyclizations involving **68** and the acetal **47** are shown in Figure 37. Strong acidic conditions led to decomposition and no detection of thienopyrrole **13**. (Figure 37a-e). Cyclization in 25% acetic acid resulted in low yields (Figure 37f), while treatment with the unprotected aldehyde **70** at lower temperature (Figure 37g) resulted in the 4% maximum yield obtained.

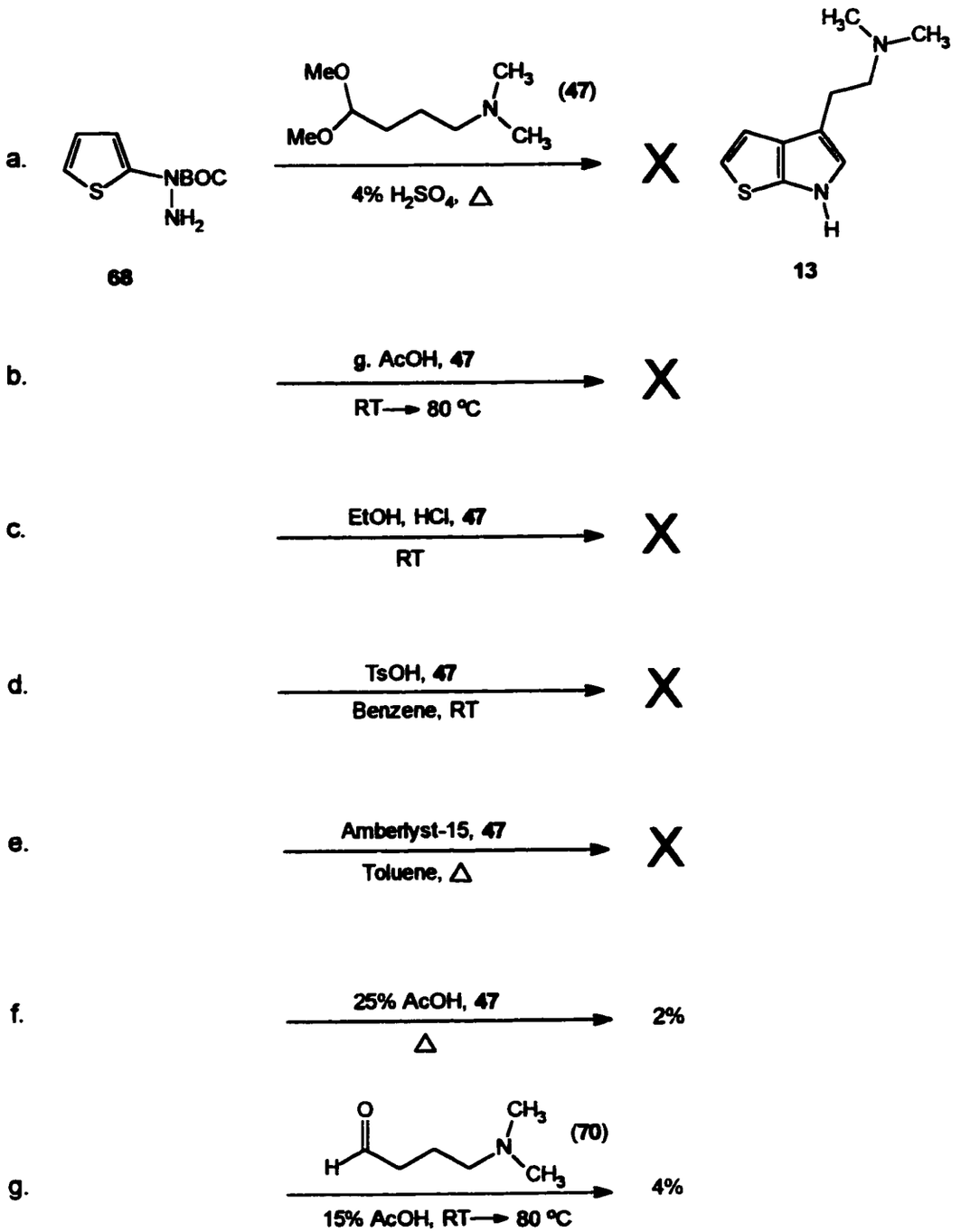


Figure 37. Attempted cyclizations of thienylhydrazines to thienopyrrole **13**.

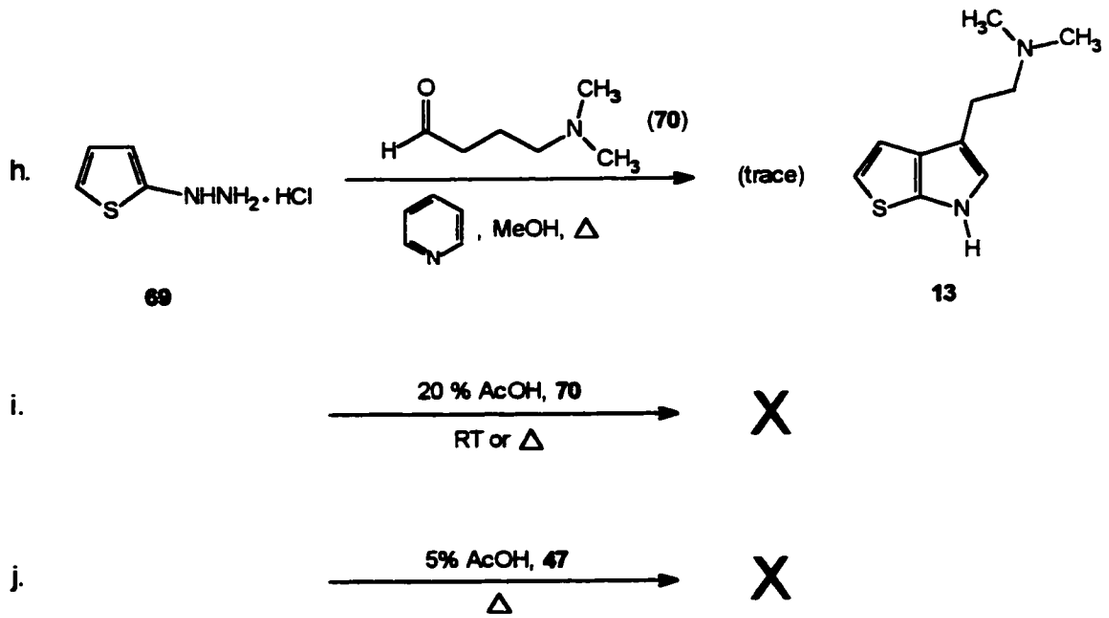


Figure 37, continued.

Deprotection of the thienylhydrazine, followed by treatment with **70** or **47** similarly produced no detectable thienopyrrole (Figure 37i, j), except when "non-acidic" Fischer indole conditions were used (Figure 37h), resulting in a trace of product. During these experiments, it became apparent that the electron-rich thienopyrrole nucleus is sensitive to acidic conditions, unless an electron withdrawing substituent is present in the resulting thienopyrrole nucleus.

A recent literature report[55] using an intramolecular palladium-catalyzed Heck cyclization[99-102] afforded an alternative approach to each of the two target compounds. Following the general procedure of Wensbo *et al.*,[55] both **77** and **86** were obtained in excellent yields, as outlined in Figures 38 and 39. The bromo isomer **83** was allylated and cyclized in comparable yield to that achieved with the iodo isomer,[55] to give **85**. The

esters **77** and **86** were then converted into the corresponding dimethylamides by treatment with methylchloroaluminum dimethylamide (**78**), prepared from commercially available trimethylaluminum and dimethylamine hydrochloride,[103] to afford amides **79** and **87** in 95 and 89% yields, respectively. Reduction of the amides was carried out with LAH in THF at reflux, leading to isolation of **12** and **13** in yields of 97 and 93%, respectively. These two products proved to be surprisingly stable, as long as mild acidic conditions were avoided.

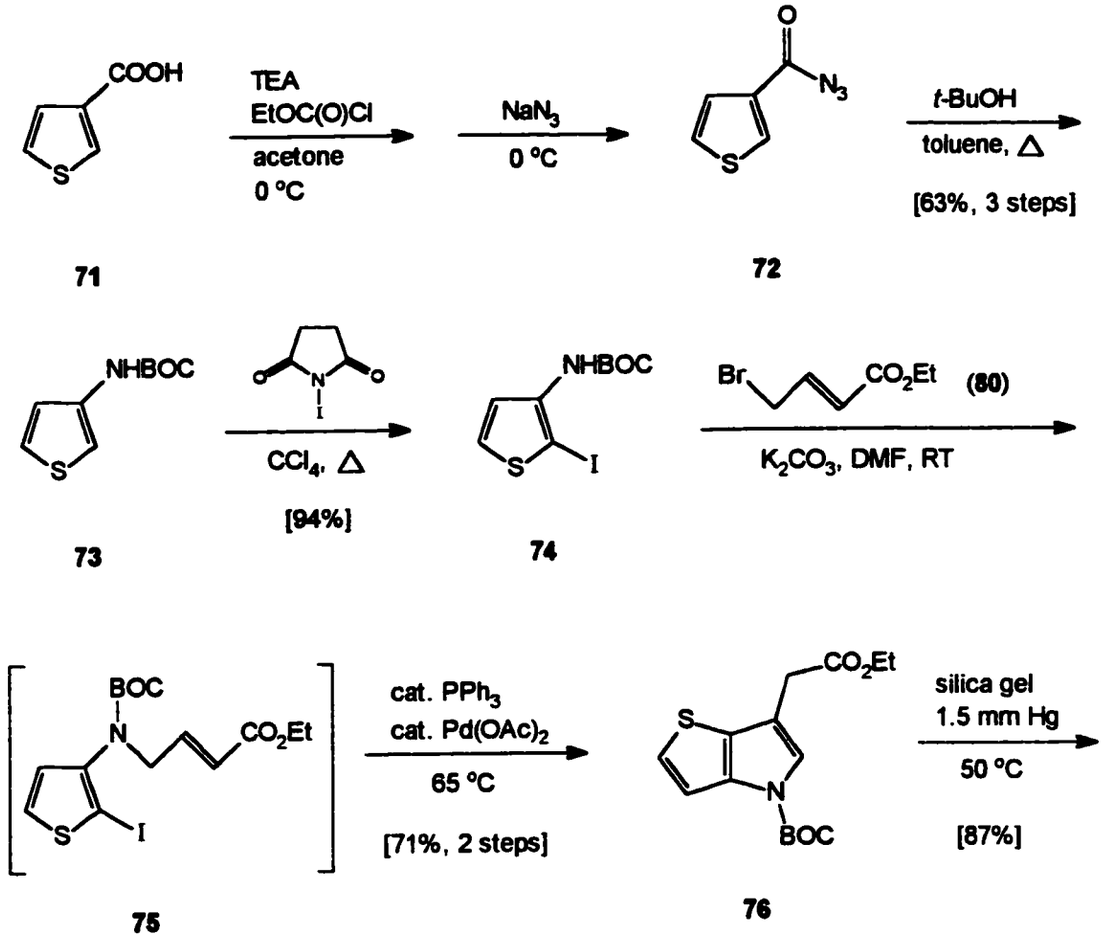


Figure 38. Synthesis of 6-(2-*N*,*N*-dimethylamino)ethyl-4*H*-thieno[3,2-*b*]pyrrole (**12**).

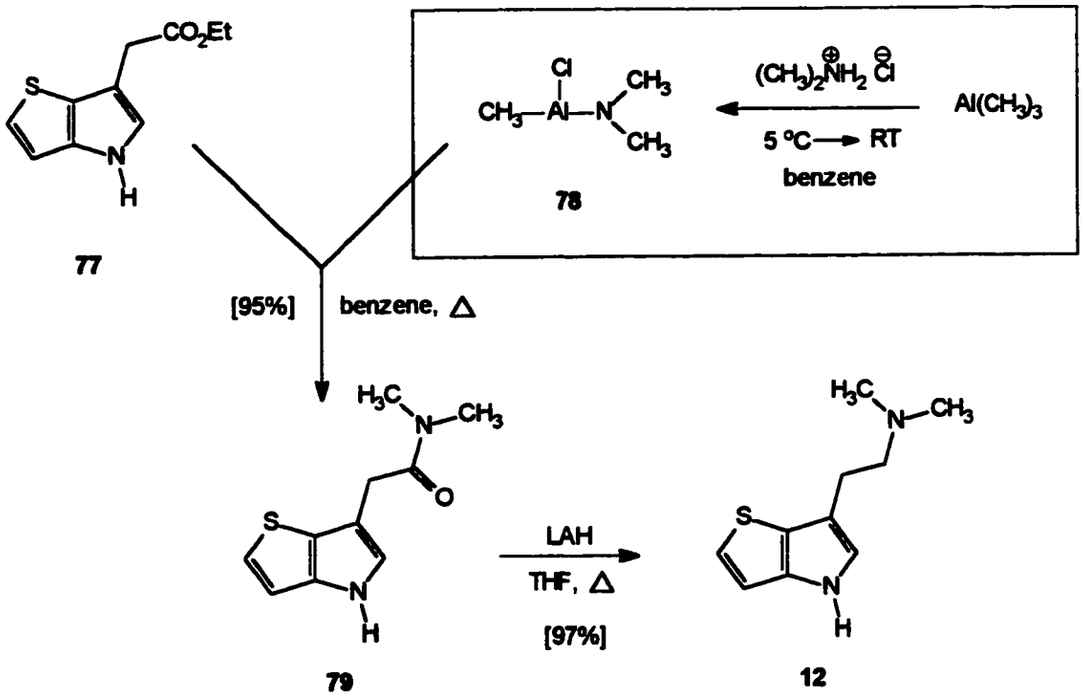


Figure 38, continued.

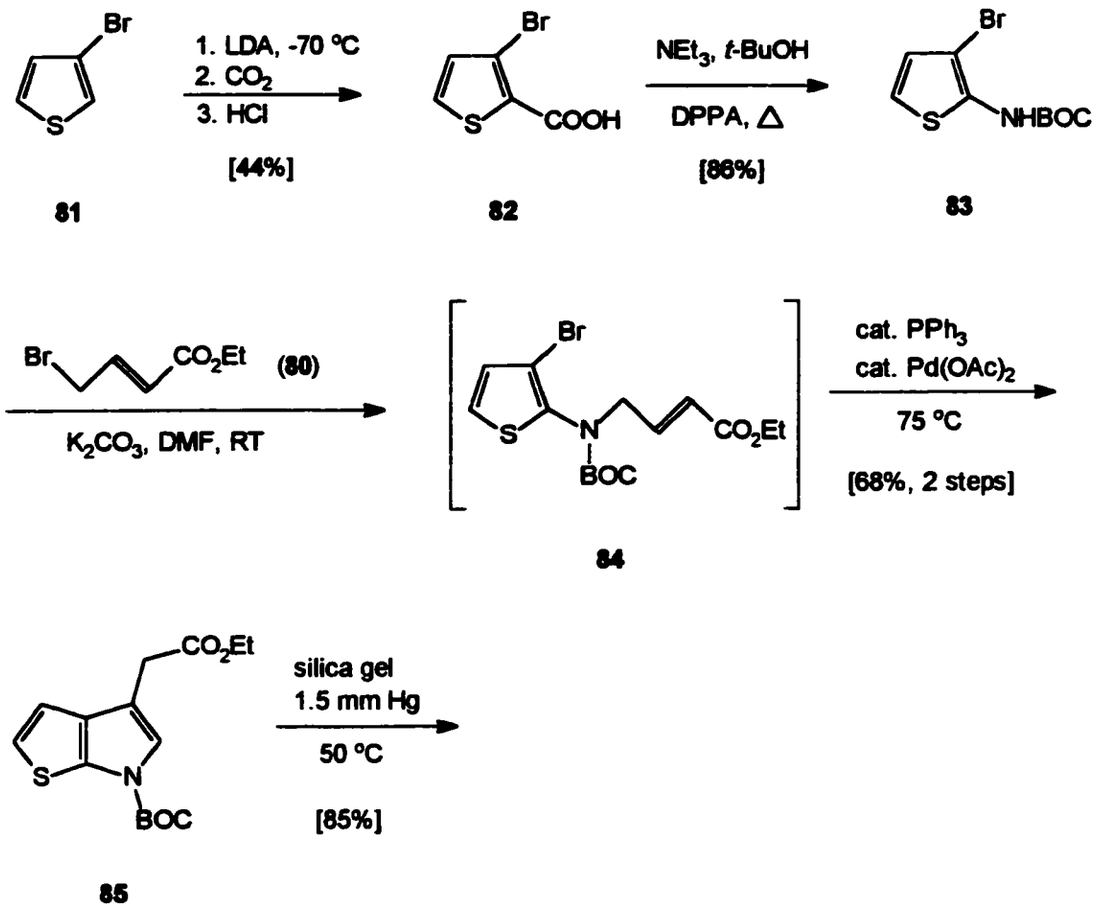


Figure 39. Synthesis of 4-(2-*N*,*N*-dimethylamino)ethyl-6*H*-thieno[2,3-*b*]pyrrole (**13**).

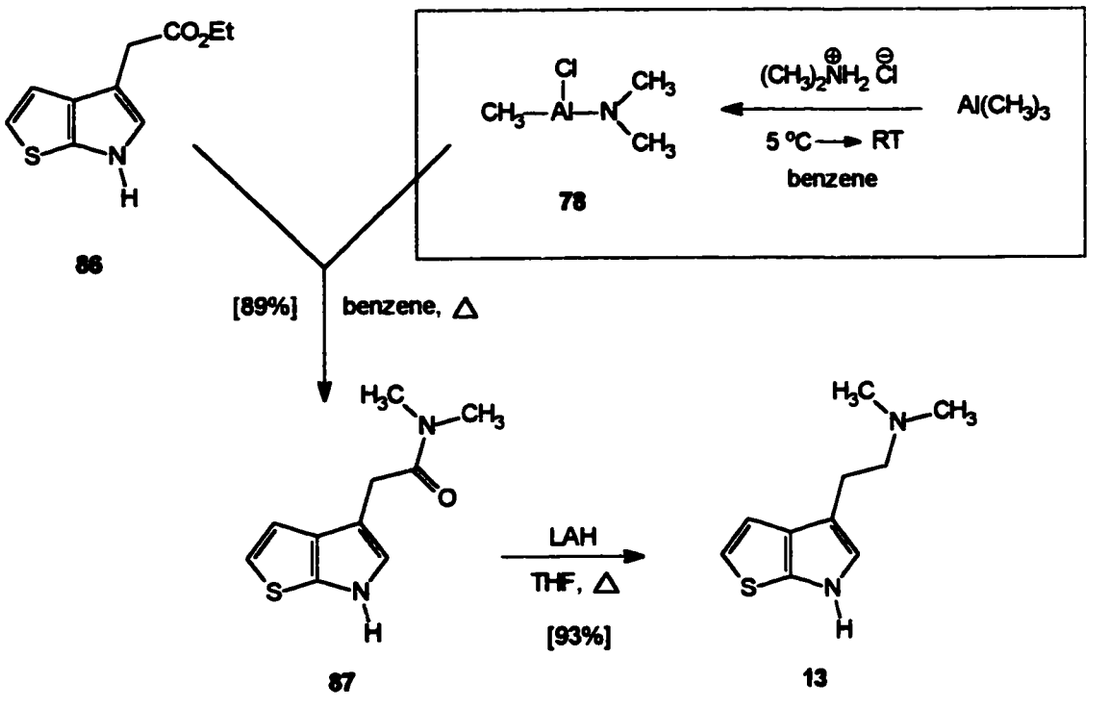


Figure 39, continued.

Pharmacology

The target compounds synthesized in this work are currently being tested *in vivo* in rats to evaluate them for hallucinogenic activity (LSD-like and 5-HT_2-mediated) and for 5-HT_{1A} activity. Also, *in vitro* receptor binding assays are used to evaluate several derivatives for 5-HT_{1A} affinity. The behavioral and receptor binding assays were performed by Danuta Marona-Lewicka and Arthi Kanthasamy, respectively, in our

laboratories, and the results presented here include those completed at the time of this writing.

Drug Discrimination

The fluorinated tryptamines are currently being evaluated in the two-lever drug discrimination (DD) behavioral assay to assess hallucinogenic activity in LSD-trained rats, 5-HT_2-mediated hallucinogenic activity in DOI-trained rats, and 5-HT_{1A} activity in LY293284-trained rats. Complete pharmacological data for the thienopyrrole analogs **12** and **13** has not yet been obtained. Details of the DD methodology have been described elsewhere.[104-108] Briefly, rats were trained to discriminate intraperitoneal (ip) injections of the training drug from saline by pressing a lever for food reinforcement. Following an ip injection of the test drug, the rat's response was measured according to the number of presses on the training drug lever, as opposed to the lever for a saline response.

The results are presented in Tables 3-5. The DD results for reference compounds are included at the beginning of each table. "PS" (partial substitution) and "NS" (no substitution) indicate that the compound did not completely substitute for the training drug. "N" is the number of rats at each dose and "% of D" represents the percentage of rats scoring as "disrupted," in which a minimum number of 50 presses was not completed on one lever within five minutes. The entry "% of SDL" equals the percentage of rats selecting the drug lever at each dose.

Table 3. Drug discrimination in LSD-trained rats.

	DOSE					ED_{50} (95% C.L.)
DRUG	**mg/kg**	**μmol/kg**	**N**	**% of D**	**% of SDL**	**μmol/kg**
LSD	0.01	0.023	13	0	31	0.037
30 min	0.02	0.046	14	7	62	(0.023-0.057)
	0.04	0.093	15	0	81	
	0.08	0.186	16	0	100	
DET	0.25	1.16	8	0	25	2.53
	0.5	2.31	9	11	64	(1.12-5.71)
	1.0	4.63	8	0	64	
	2.0	9.26	10	10	67	
	3.0	13.89	12	8	91	
Psilocin	0.125	0.61	9	11	25	1.01
	0.25	1.23	9	11	38	(0.69-1.46)
	0.375	1.84	11	18	89	
	0.50	2.45	9	11	100	
5-MeO-	0.12	0.54	9	11	25	1.49
DMT	0.24	1.08	10	10	33	(0.88-2.53)
15 min.	0.47	2.16	17	59	57	
	0.59	2.7	15	60	83	
	0.94	4.31	11	100	-	
5-MeO-	0.24	1.08	8	13	0	PS
DMT	0.47	2.16	11	18	22	
30 min.	0.94	4.31	11	27	63	
	1.41	6.47	10	40	50	
4-F-DMT	1.29	4	9	0	33	NS
(3)	2.58	8	9	11	0	
	5.16	16	9	0	56	
5-F-DMT	2.63	8	9	0	0	NS
15 min						
5-F-DMT	1.31	4	12	17	10	NS
(4)	2.63	8	15	13	15	
	5.25	16	13	8	33	
6-F-DMT	1.29	4	9	0	0	NS
(2)	2.58	8	9	0	11	
	5.16	16	9	22	29	
	10.32	32	5	60	0	
4,5-diF-	0.56	2	14	6	15	NS
DMT	1.13	4	13	8	25	
(5)	2.26	8	14	0	57	

4,7-diF-DMT (7)	1.13	4	14	0	7	NS
	2.26	8	14	0	14	
	4.52	16	16	0	19	
	9.03	32	14	0	29	
4-F-5-MeO-DMT (11)	0.037	0.125	10	0	20	NS**
	0.074	0.25	10	0	10	
	0.15	0.5	8	0	12.5	
	0.29	1.0	10	10	11	
	0.59	2.0	10	10	22	
6-F-5-MeO-DMT 30 min.	0.59	2	10	0	0	NS
	1.2	4	11	0	17	
	2.35	8	10	60	25	
	4.7	16	8	82	50	
6-F-5-MeO-DMT (10)	0.59	2	10	0	10	4.72 (3.02-7.36)
	1.2	4	11	0	45	
	2.35	8	10	10	89	
	4.7	16	8	25	86	

**4-F-5-MeO-DMT-induced a very strong 5-HT syndrome (e.g. flat body posture and lower lip retraction)

Table 4. Drug discrimination in DOI-trained rats.

	DOSE					ED_{50} (95% C.I.)
DRUG	**mg/kg**	**μmol/kg**	**N**	**% of D**	**% of SDL**	**μmol/kg**
DOI						0.30 (0.19-0.47)
4-F-DMT (3)	1.29	4	11	9	10	NS
	2.58	8	9	33	17	
	5.16	16	9	67	33	
5-F-DMT (4)	0.66	2	5	0	0	NS
	1.31	4	10	0	10	
	2.63	8	8	12.5	43	
	5.25	16	8	75	100	
6-F-DMT (2)	2.35	8	10	0	10	NS
	4.70	16	10	0	20	
	9.40	32	10	50	40	
6-F-DET (1)	0.7	2	8	0	0	NS
	1.4	4	8	20	17	
	2.8	8	8	20	33	
	3.6	16	8	20	33	

4,5-diF-DMT (5)	0.56	2	8	0	0	PS
	1.13	4	8	12.5	43	
	2.26	8	8	12.5	43	
	4.52	16	8	20	50	
	9.03	32	8	37.5	60	
4,7-diF-DMT (7)	1.13	4	8	12.5	14	NS
	2.26	8	7	28.5	40	
	4.52	16	8	0	50	
	9.03	32	7	28.5	40	
5-MeO-6-F-DMT (10)	0.59	2	6	17	20	NS
	1.18	4	12	33	50	
	2.35	8	7	86	100	
4-F-5-MeO-DMT (11)	0.037	0.125	6	0	0	PS
	0.074	0.25	6	0	50	
	0.15	0.5	6	33	50	
	0.29	1.0	6	50	66	
	0.59	2.0	6	33	25	
	1.18	4.0	6	67	0	

Table 5. Drug discrimination in LY293284-trained rats.

	DOSE					ED_{50} (95% C.I.)
DRUG	**mg/kg**	**μmol/kg**	**N**	**% of D**	**% of SDL**	**μmol/kg**
LY293284						0.031 (0.02-0.05)
8-OH-DPAT						0.099 (0.056-0.17)
4,5-diF-DMT (5)	0.28	1	12	17	10	PS
	0.56	2	10	10	33	
	1.13	4	14	7	69	
	2.26	8	10	40	50	
	4.52	16	11	55	40	
4,7-diF-DMT (7)	1.13	4	11	0	18	NS
	2.26	8	11	0	27	
	4.52	16	11	0	36	
4-F-5-MeO-DMT (11)	0.037	0.125	13	15	27	0.17 (0.13-0.2)
	0.074	0.25	14	0	79	
	0.15	0.5	13	38	100	

Body Temperature and the "Serotonin Syndrome"

The fluorinated tryptamines were evaluated for their ability to reduce body temperature, as a further verification of 5-HT_{1A} activity. Briefly, male Sprague-Dawley rats (175-250 g) were purchased from Harlan, Indianapolis, IN and were acclimated to the housing environment for at least 1 week before testing. Body temperature was measured with a CMA/150 Temperature Controller (Carnegie Medicin, Stockholm, Sweden) by lubricating the probe tip with mineral oil and inserting it approximately 3 cm into the rectum for 10 to 15 sec. Measurements were taken 10 min and just before compound administration and in 10 min intervals for 90 min after s.c. treatment. The changes in body temperature were evaluated by determining the differences in temperature after treatment compared with the pretreatment values. The results are displayed in Figure 40.

Another indication of 5-HT_{1A}-mediated activity is the visually observable "serotonin syndrome" which includes lower lip retraction (LLR), flat body posture, and forepaw treading. Rats were acclimated to the housing environment for at least 1 week before testing. The lower lip retraction response was evaluated using a 0 to 1 scale (0 - lower incisors not or hardly visible, 0.5 - partly visible, 1 - completely visible). The flat body posture and forepaw treading were evaluated using a 0 to 1 scale (0 - non, 0.5 - present, 1 - intensive). The behavioral evaluations were made at 10 min intervals, ending 90 min after s.c. treatment. The data are presented as apercentage of the total maximum score from 7 animals/dose/drug. The results are presented in Figures 41-43.

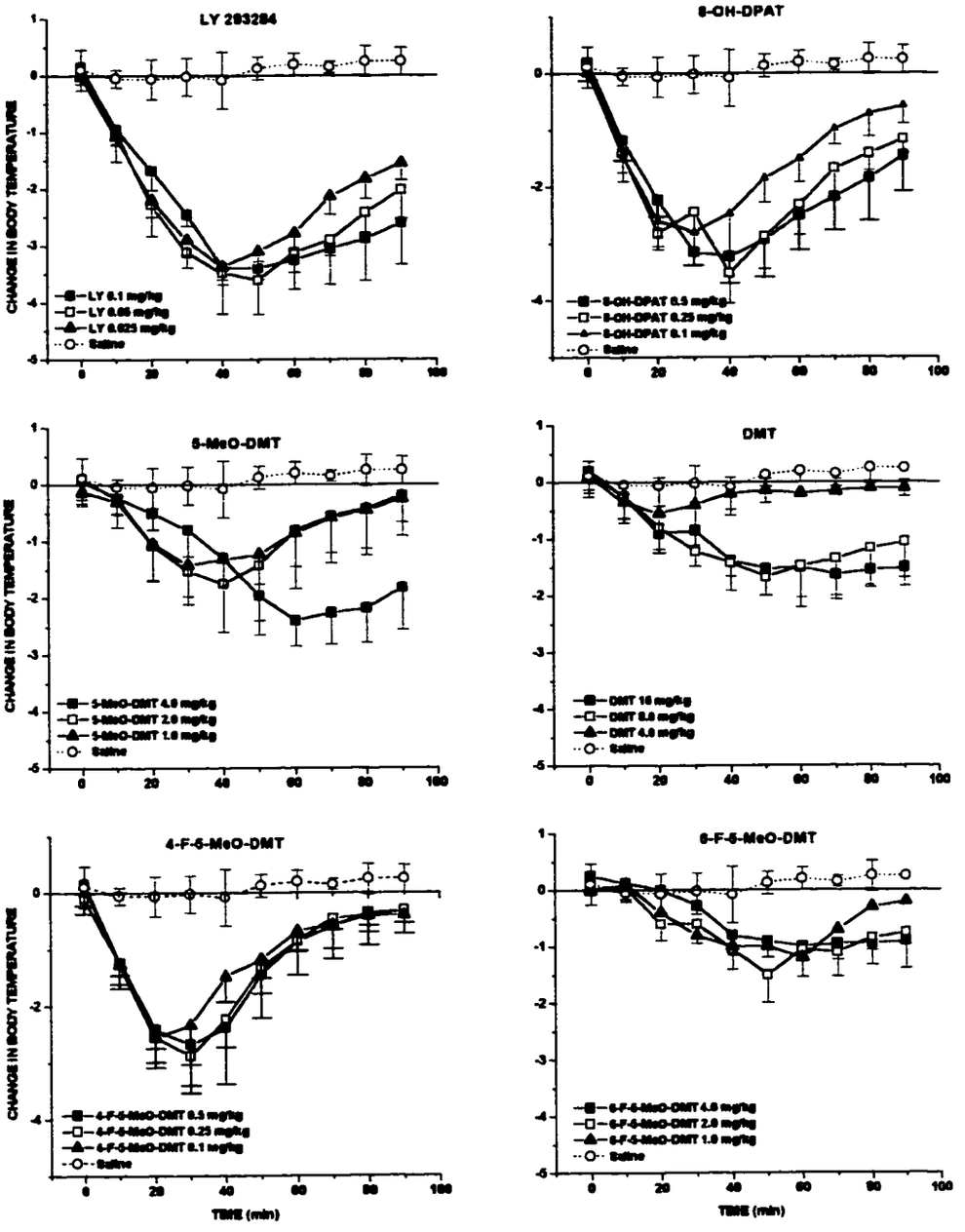
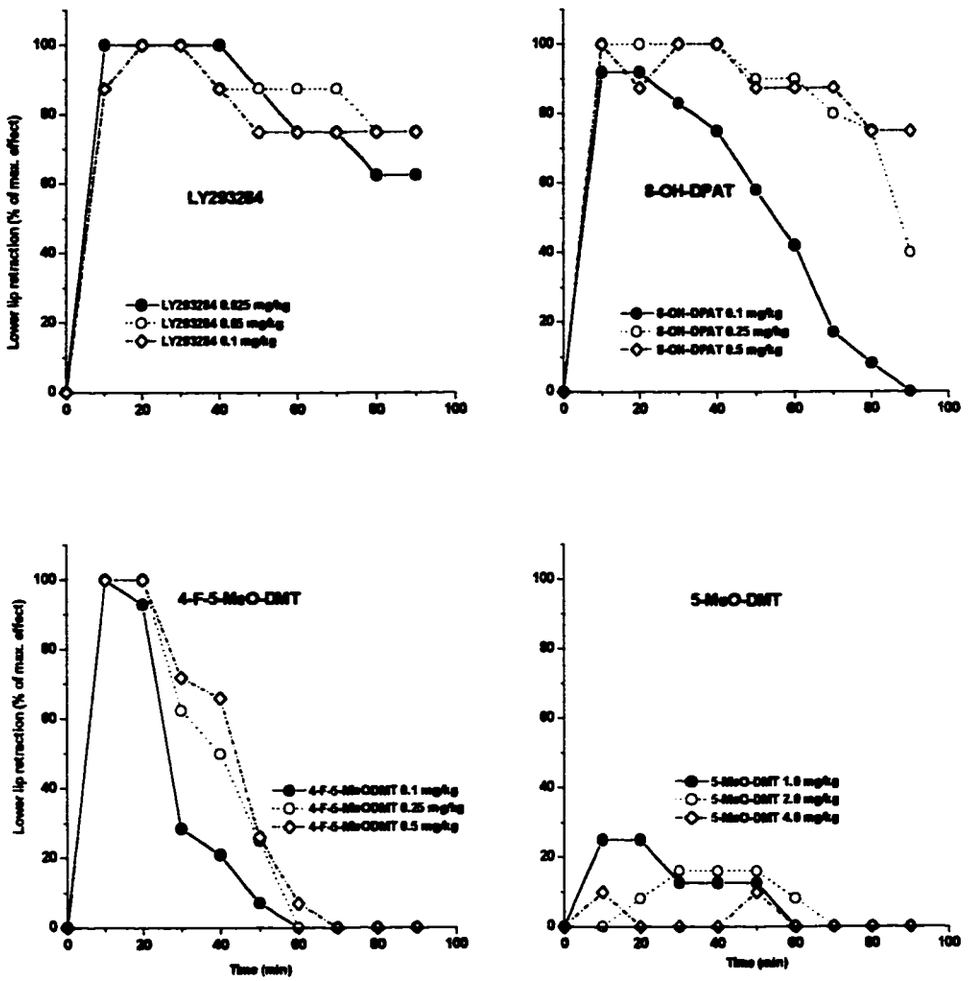
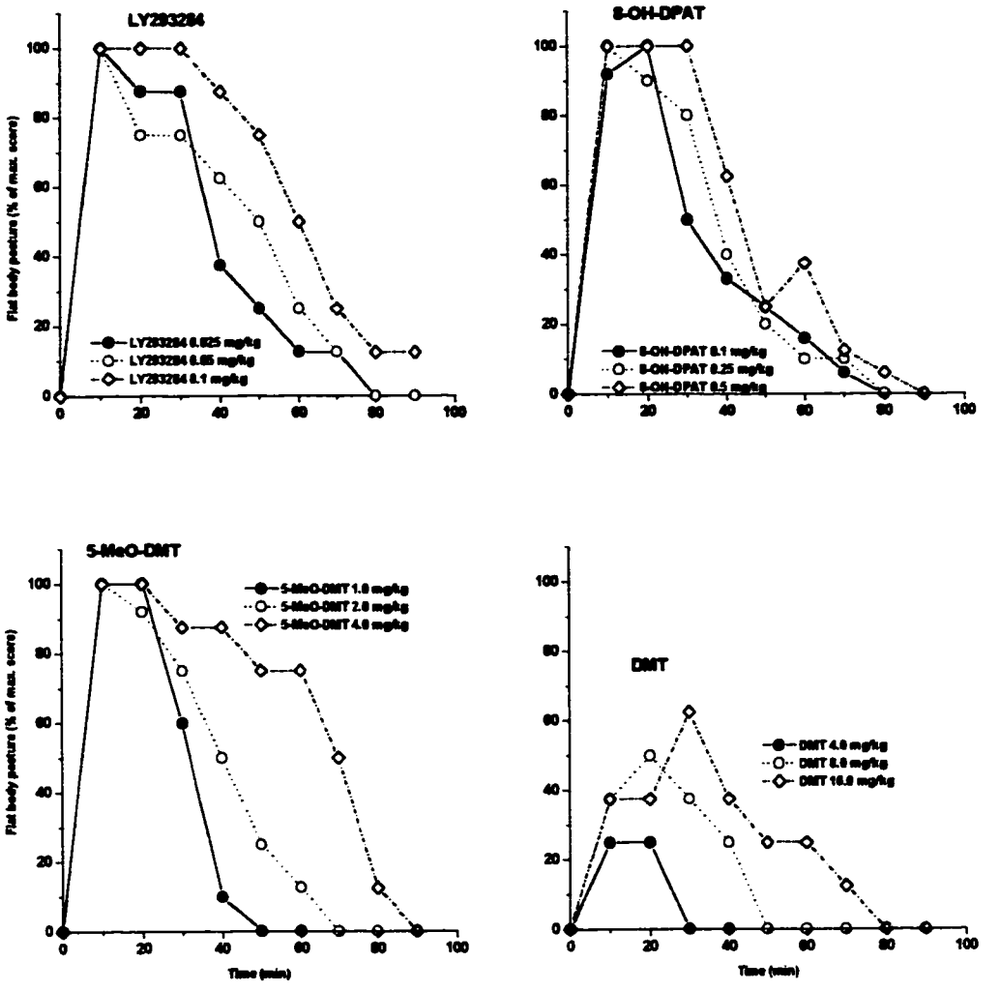


Figure 40. Change in body temperature after drug administration.



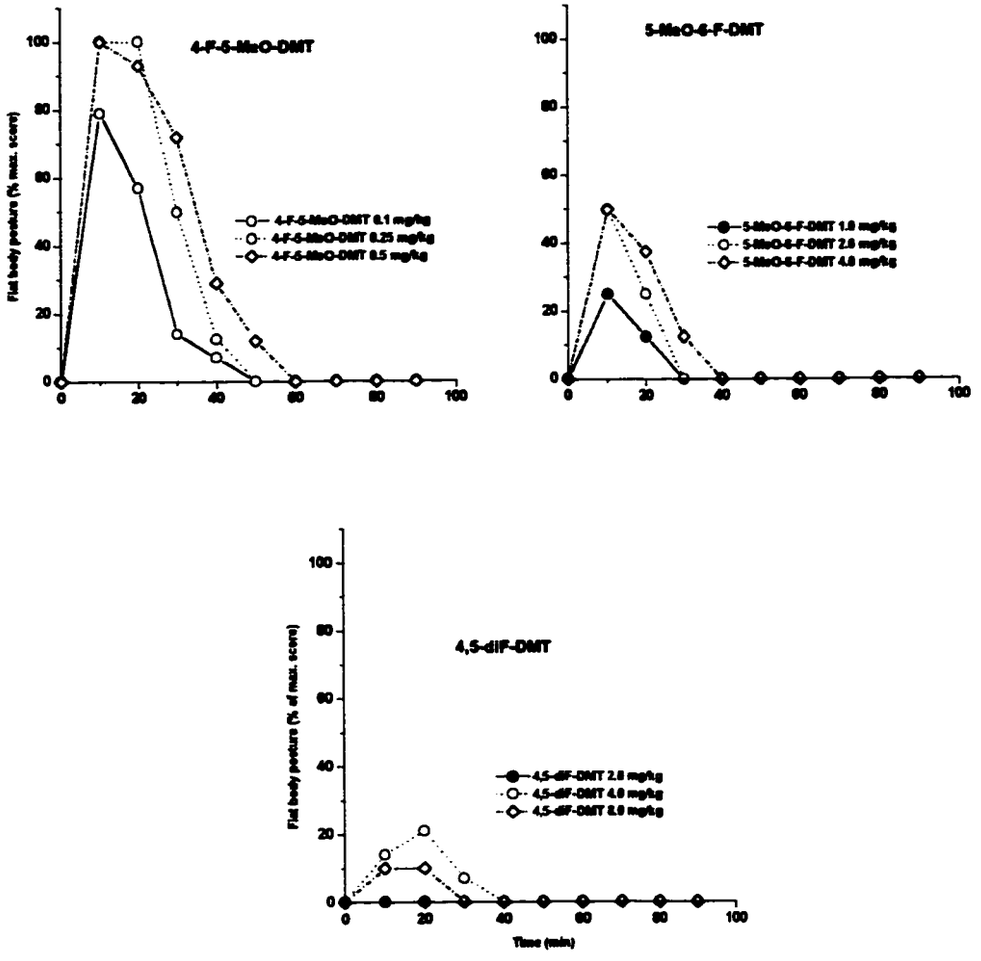
Effects of LY293284, 8-OH-DPAT, 4-F-5-MeO-DMT, and 5-MeO-DMT on lower lip retraction in male rats (7 animals/dose)

Figure 41. Lower lip retraction results.



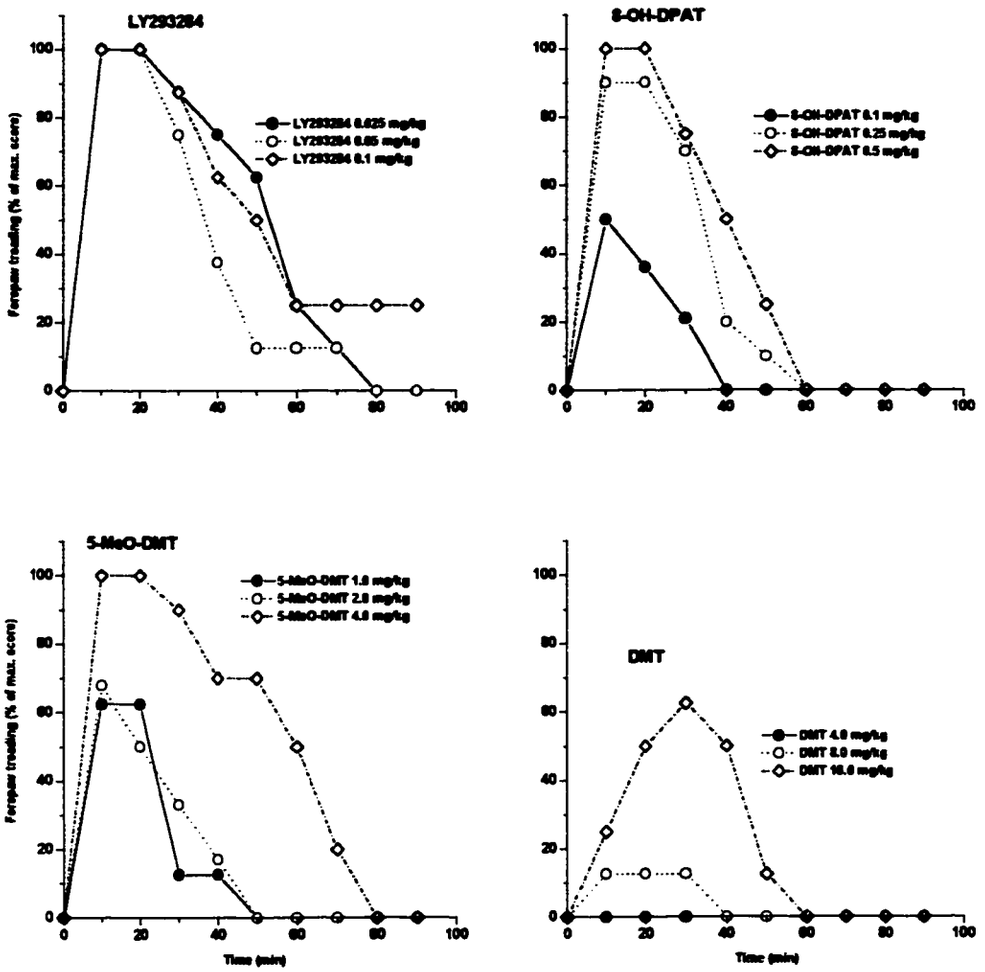
Effects of LY2933284, 8-OH-DPAT, 5-MeO-DMT, and DMT on flat body posture in male rats (7 animals/dose)

Figure 42. Flat Body Posture.



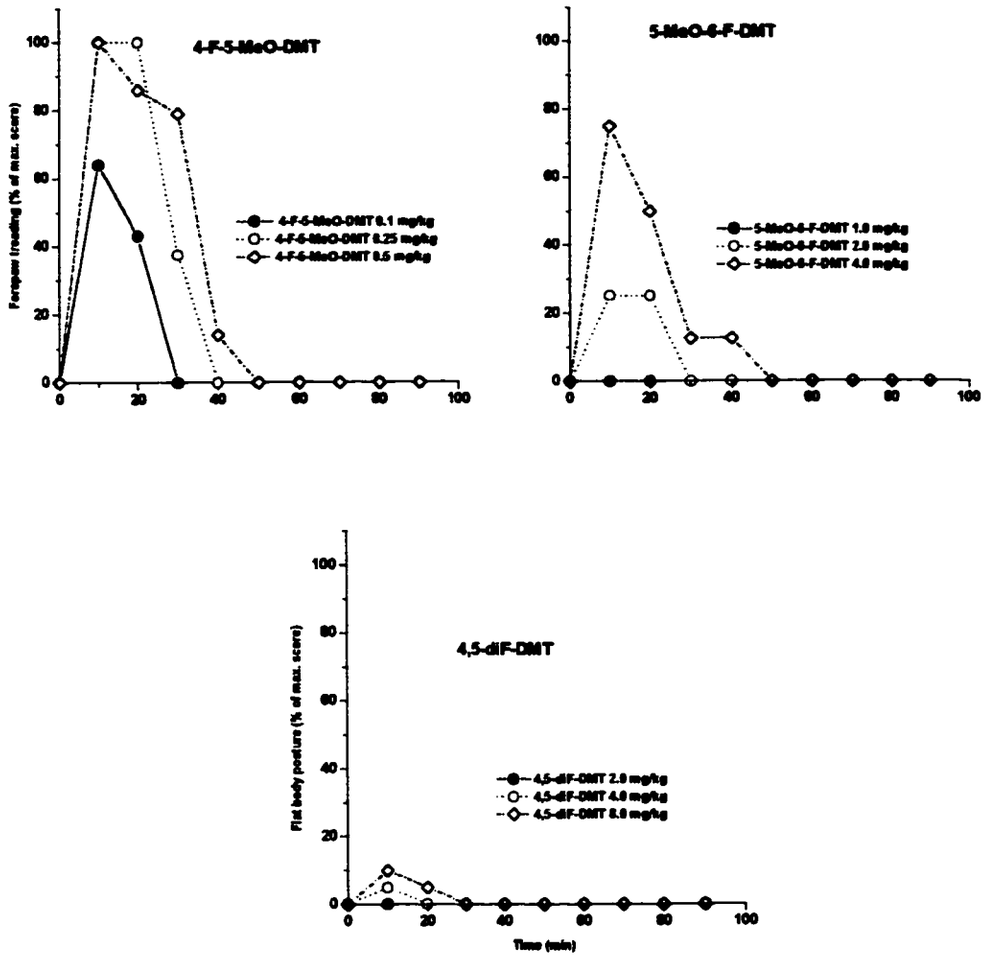
Effect of 4-F-5-MeO-DMT, 5-MeO-6-F-DMT, and 4,5-diF-DMT on flat body posture in male rats (7 animals/dose)

Figure 42, continued.



Effects of LY2933284, 8-OH-DPAT, 5-MeO-DMT, and DMT on forepaw treading in male rats (7 animals/dose)

Figure 43. Forepaw treading.



Effect of 4-F-5-MeO-DMT, 5-MeO-6-F-DMT, and 4,5-diF-DMT on forepaw treading in male rats (7 animals/dose)

Figure 43, continued.

Receptor Binding

Several fluorinated tryptamines were evaluated in preliminary studies for affinity at the 5-HT_{1A} receptor site in rat hippocampal tissue preparations by displacement of the radioligand [^{3}H]8-OH-DPAT. Details of the radioligand competition methodology can be found elsewhere.[107,108] Table 6 lists the K_i values for compounds **3**, **8**, **10**, and **11**, as well as psilocin and other literature reference compounds for comparison. Further studies of the fluorinated tryptamines and thienopyrrole analogs at the 5-HT_{1A} and 5-HT_{2A} receptor sites will be completed in the near future. The 5-HT_{2A} affinities of 5-MeO-DMT and 8-OH-DPAT are included to show the nonselectivity and selectivity, respectively, of these two reference compounds.

Table 6. K_i values for serotonin 5-HT_{1A} (displacement of [^{3}H]8-OH-DPAT) and 5-HT_{2A} (displacement [^{3}H]ketanserin and [^{125}I]DOI) receptors; expressed in nM affinity.

	5-HT_{1A}(8-OH-DPAT)	5-HT_{2A}(ket)	5-HT_{2A}(DOI)
4-F-5-MeO-DMT[a] (11)	3.81 ± 0.14		
4-F-DMT[a] (3)	135 ± 9		
Psilocin[a]	378 ± 47		
6-F-Psilocin[a] (8)	590 ± 24		
6-F-5-MeO-DMT[a] (10)	998 ± 130		
DMT[b]	245		
5-HT[c]	1.7		
5-MeO-DMT[d]	1.9		
5-MeO-DMT[c]	7.8	620	15
5-MeO-DMT[e]	10		
8-OH-DPAT[c]	2	5350	635
8-OH-DPAT[d]	0.56		
(R) Pyrrolidine Analog[f]	10	730	17

a. Nichols *et al.*, (1997, unpublished); rat hippocampal tissue
b. Nelson *et al.*, (1987); Tissue used: cortex dorsal to rhinal sulcus (rat).[109]
c. Glennon *et al.*, (1988); Rat hippocampal tissue.[110]
d. Peroutka *et al.*, (1986); Rat frontal cortex tissue.[111]
e. Glennon *et al.*, (1989); Rat hippocampal tissue.[112]
f. Macor *et al.*, (1992); See Introduction and Figure 3.[11]

CONCLUSIONS

The fluorinated tryptamine derivatives and thienopyrrole analogs of DMT presented in Figure 21 were synthesized and are currently being evaluated behaviorally *in vivo* and assayed for *in vitro* activity at serotonin receptors. The preparation of tryptamines **1**, **2**, **8**, and **9** included a novel decarboxylation method developed in our laboratory using *N*-methylpyrrolidinone as the solvent and with concurrent purging of the refluxing reaction mixture with inert gas. In addition, 6-fluoro-psilocin was finally accessible due to recent development of the Hemetsberger methodology[64-68] for the synthesis of indoles, along with an *ortho*-specific formylation procedure recently reported in the literature for the synthesis of fluorinated salicylaldehydes.[71] Compounds **3-7**, **10**, and **11** were prepared via Fischer indole cyclization procedures. Due to the failed Fischer indole cyclizations in the synthesis of the thienopyrrole analog **13**, the acetate esters **77** and **86** were prepared in excellent yield following the general procedure of Wensbo *et al.*[55] In the case of derivative **13**, the more accessible bromo intermediate **83** was allylated and cyclized in comparable yield to that achieved with the iodo isomer,[55] to give **85**. The syntheses of **12** and **13** were then completed through the formation of the amides followed by reduction with LAH.

Tables 3-5 list the drug discrimination results completed for the fluorinated tryptamines at the time of this writing. It is evident from these results that fluorination of tryptamines in the 4, 5, 6, and 7 positions generally attenuates or abolishes hallucinogenic activity. Only 6-fluoro-5-methoxy-DMT (**10**) generalized to the LSD cue with an ED_{50} of

4.72 μmol/kg (Table 3). In DOI-trained rats 4,5-difluoro-DMT (**5**) and 4-fluoro-5-methoxy-DMT (**11**) only partially substituted for the training drug (Table 4). Therefore, only **10** displayed "hallucinogenic" activity in the behavioral studies, with an ED_{50} approximately 3-fold higher than 5-methoxy-DMT (ED_{50} = 1.49 μmol/kg) in the LSD-trained rats. Since hallucinogenic activity is generally thought to be mediated by 5-HT_2 receptors,[17] fluorination appears to attenuate affinity for this receptor subtype. Radioligand competition studies to evaluate affinities at 5-HT_2 receptor sites are pending at the time of this writing.

An interesting discovery was made in the evaluation of compound **11**. Although this analog did not substitute for LSD, it produced in the rats an observable "serotonin syndrome" characteristic of 5-HT_{1A} agonist activity, which includes flat body posture, lower lip retraction (LLR), and forepaw treading. This derivative was also found to produce hypothermia in the rats. Activation of central 5-HT_{1A} receptors produces hypothermia in laboratory animals whereas systemic administration of 5-HT_2 agonists evokes a hyperthermic response. The results are presented in Figure 40 and show that **11** (4-fluoro-5-methoxy-DMT) produced a lowered body temperature in the animals similar to the standard 5-HT_{1A} agonists 8-OH-DPAT and LY293284. The LLR, flat body posture, and forepaw treading behavioral results are presented in Figures 41, 42, and 43, respectively. As with the hypothermia results, **11** produces these 5-HT_{1A} mediated behaviors as intensely as the standard compounds 8-OH-DPAT and LY293284, with comparable doses to 8-OH-DPAT in all four studies

In addition, the drug discrimination studies in LY293284-trained rats (Table 5), which evaluates for 5-HT_{1A} activity, confirmed these observations. Although fluorinated derivatives 4,5-difluoro-DMT (**5**) and 4,7-difluoro-DMT (**7**) displayed partial and no substitution, respectively, 4-fluoro-5-methoxy-DMT (**11**) fully substituted for the training drug with an ED_{50} comparable to the standard 5-HT_{1A} agonist 8-OH-DPAT. The high 5-HT_{1A} activity of **11** was unexpected since 4-oxygenation (i.e. psilocin) produces selectivity for 5-HT_{2A} receptors,[17] and fluorine can sometimes be considered an bioisosteric replacement for a hydroxy group. As with the dramatic loss of activity of DET with 6-fluorination (abolishment of hallucinogenic activity), 4-fluorination also dramatically alters the activity of 5-methoxy-DMT, in this case presumably resulting in an increase in affinity for the 5-HT_{1A} receptor.

Preliminary radioligand competition studies at [^{3}H]-8-OH-DPAT-labeled 5-HT_{1A} receptor sites confirm the high affinity of **11** for this serotonin receptor subtype. The K_i value of **11** is 3.8 nanomolar, nearly as potent as 8-OH-DPAT (K_i = 2 nanomolar, Table 6). In addition, **11** displayed an approximately 260-fold increase in affinity compared to **10**. 4-Fluoro-DMT (**3**) and 6-fluoro-psilocin (**8**) also displayed nearly a 3-fold increase in affinity and a 2-fold decrease in affinity, respectively, compared to psilocin. Thus 4-fluorination seems to increase 5-HT_{1A} and reduce 5-HT_2 activity while 6-fluorination attenuates affinity for both 5-HT_{1A} and 5-HT_2 receptors. This evidence for the first time explains at least in part the inactivation of 6-fluoro-DET as a hallucinogen reported by Szara *et al.*[43] in 1963.

What effects could 4-fluorination have on the molecule to produce such a potent, selective 5-HT_{1A} receptor ligand in compound **11**? In general, substitution at the 5-position of indole ethylamines is required for high 5-HT_{1A} activity but not necessarily selectivity, with the carboxamido group resulting in the highest affinity. Figure 44 lists selected ligands with high 5-HT_{1A} affinity.[113] Substitution in the 8-position of aminotetralins such as the hydroxy in 8-OH-DPAT is necessary for high 5-HT_{1A} activity.[114] C(8) of the aminotetralins is speculated to be equivalent to C(5) of indoles.

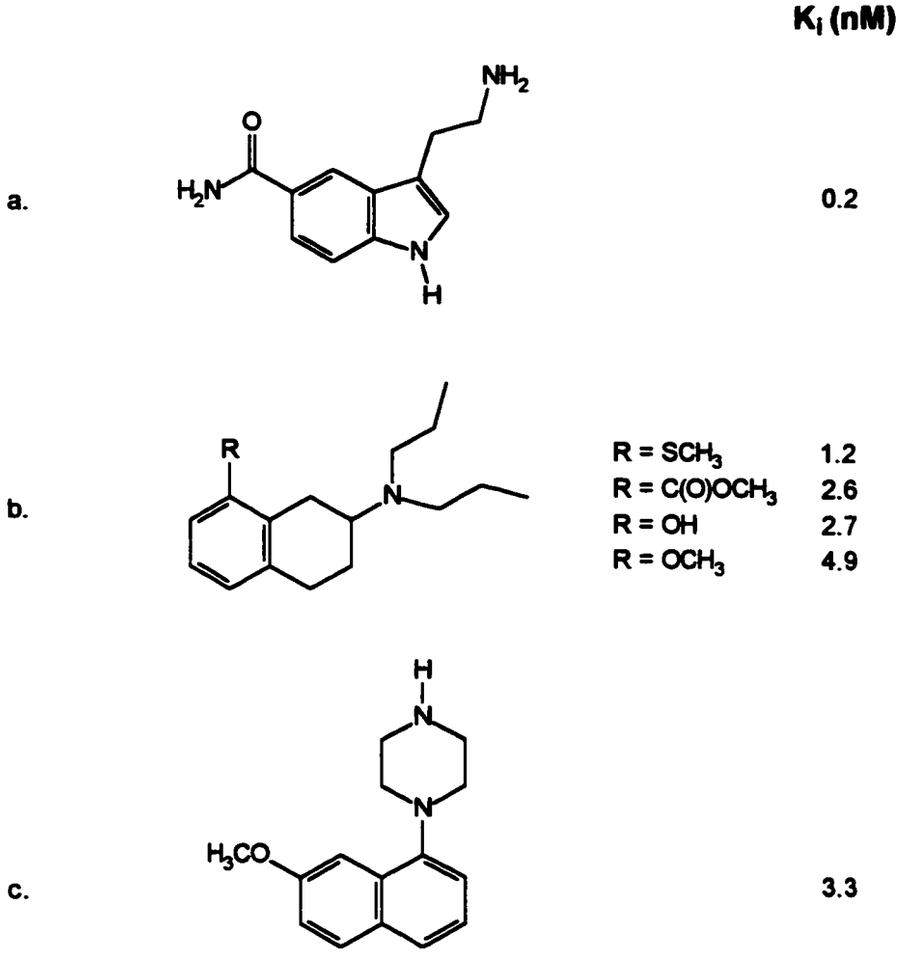


Figure 44. 5-HT_{1A} affinity of selected ligands: a) an indole ethylamine, b) aminotetralins, and c) an arylpiperazine.[113]

There are several effects fluorine could induce to cause an alteration in molecular recognition. Fluorine may induce a optimum side chain conformation by forming a hydrogen bond with the protonated side chain amine (Figure 45a). This would result in an 8-membered ring and would place the amine approximately in the same position as N(6) of the ergolines, such as LSD (see Figure 2). Fluorine may also induce an optimum 5-methoxy conformation by forming a hydrogen bond with one of the methoxy hydrogens. However, calculations (unpublished data) indicate the conformer shown in Figure 45b to be stabilized by only ~0.4 kcal/mole. In addition, this conformation would be expected to *increase* 5-HT_{2A} activity, due to similarities with the tetrahydropyrano derivative synthesized by Macor *et al.*[20], shown in Figure 7b.

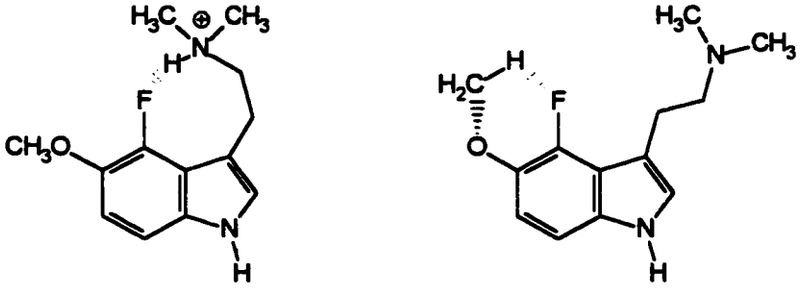


Figure 45. Possible conformations induced by fluorine.

Fluorine may also be involved in a dipole-dipole interaction possibly with an amide function in the receptor pocket, due to the partial dipole of the C-F bond. The *overall* dipole of 4-fluoro-5-methoxyskatole (calculated with Spartan software on a silicon graphics workstation) is shifted significantly from the overall dipole of 6-fluoro-5-methoxyskatole (Figure 46). Fluorination in different positions, therefore, may alter the binding orientation of the indole nucleus.

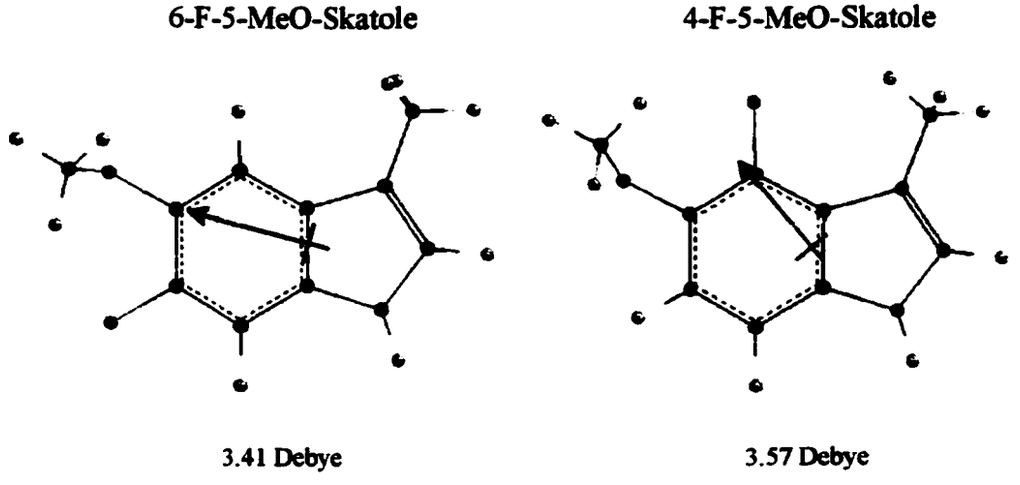


Figure 46. Shift in overall dipole produced by 4-F- vs 6-F-substitution.

Fluorine may also increase affinity by optimizing the electrostatic potential surface of a molecule. The electrostatic potential surfaces (calculated with Spartan software) for 4-hydroxy-skatole, 4-fluoro-5-methoxy-skatole, and 5-methoxy-skatole are displayed in Figure 47. Oxygenation at the 4-position of tryptamines (i.e. psilocin) results in selectivity for 5-HT_2 receptors, while 5-methoxy-DMT is nonselective. However, we now know that

4-fluoro-5-methoxy-DMT is selective for 5-HT_{1A} receptors. Although it can be seen from the molecular electrostatic potential surfaces in Figure 47 that the fluorine may be able to attract or stabilize a positive charge, as indicated by red shades in the color scheme, it is not intuitively obvious that there is a large enough change in the overall electrostatic potential to cause the dramatic increase in 5-HT_{1A} affinity with 4-fluoro-5-methoxy substitution.

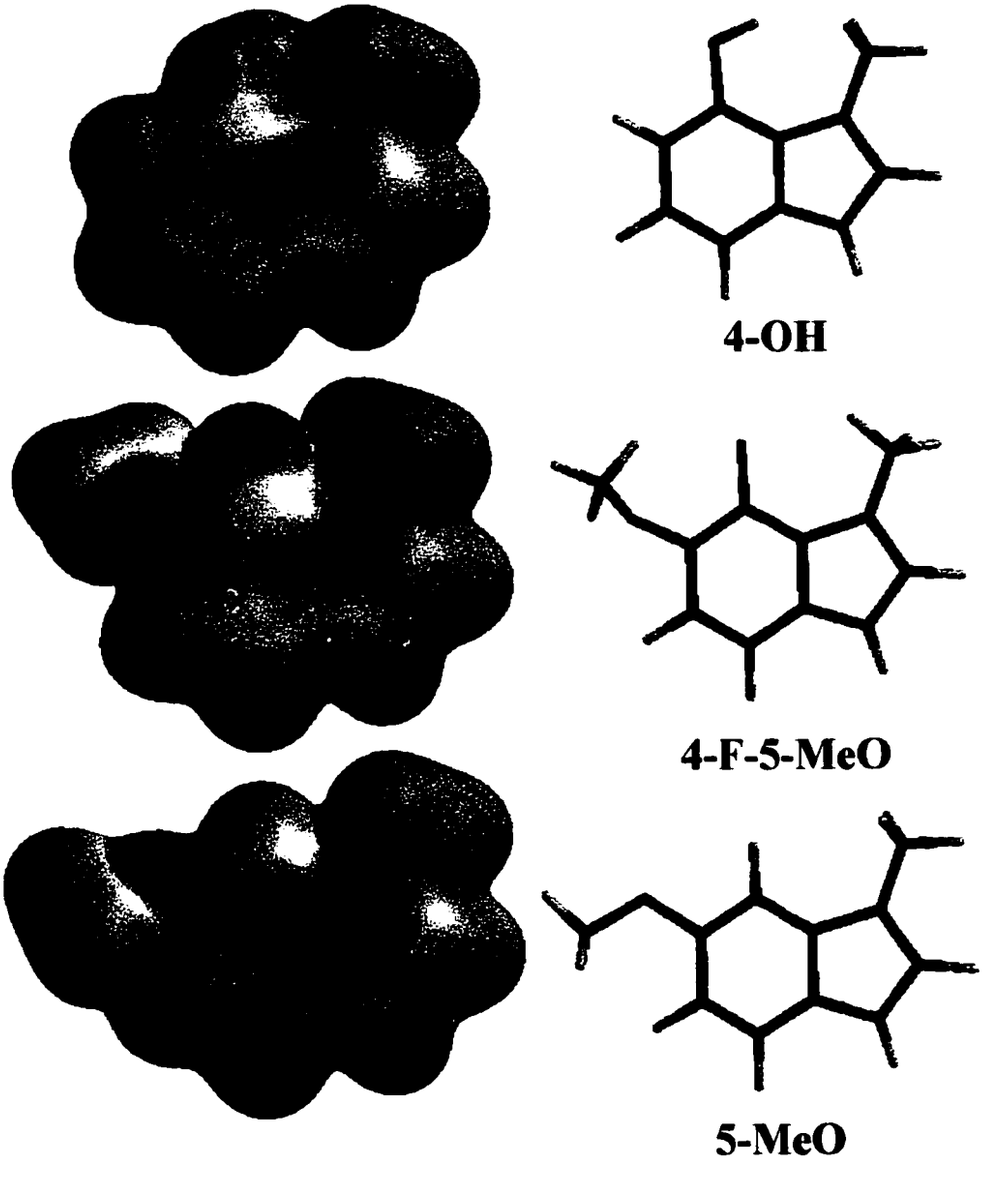


Figure 47. Electrostatic potential surfaces: 5-HT_{2A} vs 5-HT_{1A} selectivity.

Another interesting possibility arises from the ability of fluorine to participate in a hydrogen bonding interaction (discussed in more detail in the introduction). Fluorine hydrogen bonds can vary in strength from 1.48 to 3.53 kcal/mole,[37,38] up to approximately half the strength of an oxygen hydrogen bond. A fluorine hydrogen bond may therefore contribute significantly to the molecular recognition of certain tryptamines at serotonin receptors. In order for a fluorine hydrogen bond to form, the fluorine substituent must be directed optimally toward a hydrogen bond acceptor in the receptor pocket.

One possible binding model for **11** in the 5-HT_{1A} receptor pocket is shown in Figure 48, which is modified from the original model of Kuipers *et al.*[26] The hydrogen bonds to the 5-methoxy and indole N(1)H are preserved, as well as the ionic interaction with the side chain amine. Since the 3-dimensional structure of the receptor pocket is not known, it is difficult to acertain toward which TMD the fluorine is directed. Most likely, however, a hydrogen bond donor in this model would need to reside in TMD 5, 6, or 7. An analysis of the amino acid sequences of these TMD regions[115] reveals several candidates for hydrogen bond donors, including Thr^{196} in TMD 5, Thr^{353} in TMD 6, Ser^{391} in TMD 7 and Ser^{393} in TMD 7. One of the hydrogen bonding interactions in this model could explain the increased affinity of **11** for the 5-HT_{1A} receptor.

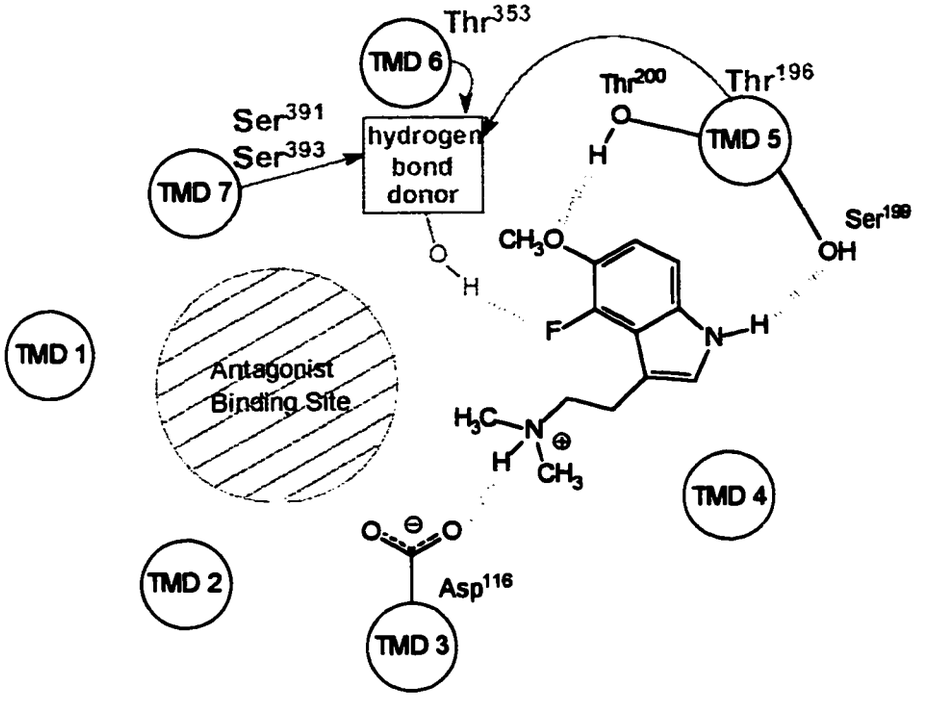


Figure 48. Proposed model for the binding of **11** at the 5-HT_{1A} receptor.

On the other hand, **11** may be rotated ~180° in the receptor pocket as shown in Figure 49. It is not entirely known in which *orientation* tryptamines bind to serotonin receptors. As discussed in the introduction, there is controversy concerning the orientation of ligand binding to the 5-HT_2 receptor subtype. Likewise, the orientation of tryptamine or ergoline binding in Kuipers' model of the 5-HT_{1A} receptor pocket is not known. It is entirely possible that Thr^{200} is hydrogen bonded to the indole N(1)H (Figure 49) rather than to the 5-methoxy (Figure 48). In this case, the 5-methoxy would be hydrogen bonded to Ser^{199}, and the ionic interaction between the protonated side chain amine and Asp^{116} is preserved. In this binding model, the fluorine appears to be directed

toward TMD 4. Analysis of the amino acid residues in TMD 4 reveals two candidates for hydrogen bond donors in Thr^{160} and Ser^{168}.

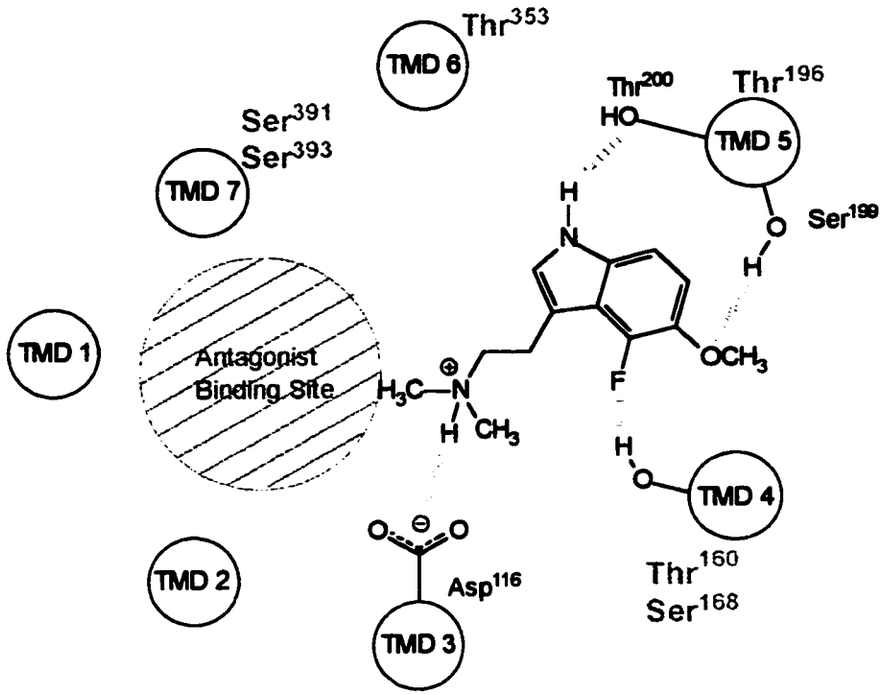


Figure 49. Alternative orientation for the binding of **11** at the 5-HT_{1A} receptor.

In addition to the altered orientation of binding in the model shown in Figure 49, the indole nucleus is necessarily shifted toward TMD 6 with respect to the binding in Figure 44 in order to accommodate the hydrogen bonds to Thr^{200} and Ser^{199}. This is due to the fact that the 5-methoxy extends away from the molecule by one bond length, and the indole nucleus is therefore shifted toward the N(1)H hydrogen bond interaction. This results in more space between the indole nucleus and TMD 4, possibly allowing a fluorine

hydrogen bond interaction that would not be possible with a residue in TMD 4 in the opposite binding orientation.

In any case, fluorination of 5-methoxy-DMT in the 4-position results in a selective, potent ligand for the 5-HT_{1A} receptor. As with fluorination in the 6-position of DET and other hallucinogens, 4-fluorination appears to be an important element in the molecular recognition of tryptamines at serotonin receptor sites and also in the mechanisms involved in hallucinogenesis. The revised models proposed in Figures 48 and 49 should aid in the development of future derivatives, especially for the tryptamine class of hallucinogens, since **11** is, to the author's knowledge, the first example of a fluorinated tryptamine with high selectivity for the 5-HT_{1A} receptor. In addition, the specific hydrogen-bonding interaction proposed could be investigated by site-specific mutations at Thr^{160} and Ser^{168} in TMD 4 of the cloned 5-HT_{1A} receptor in conjunction with radioligand competition studies to evaluate the affinity of **11** for the wild type and mutated receptors.

EXPERIMENTAL

Starting materials, solvents and reagents were purchased commercially, except where noted. All ^{1}H NMR spectra were recorded on a Bruker ARX 300-MHz instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane (TMS) in $CDCl_3$, except where noted. Abbreviations used to report NMR peaks are as follows: br s = broad singlet, d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, s = singlet, t = triplet, td = triplet of doublets. Melting points were determined with a Thomas-Hoover Meltemp apparatus and are uncorrected. Analytical thin-layer chomatography (TLC) was performed on Baker-Flex silica gel 1B2-F plastic plates. Chemical ionization mass spectra (CIMS) were determined on the Purdue University Department of Medicinal Chemistry and Molecular Pharmacology's Finnegan 4000 quadrupole mass spectrometer, using isobutane as the reagent gas and are reported as m/e (relative intensity). Elemental analyses were obtained from the Purdue Microanalysis Laboratory and all of the results are within 0.4% of the calculated values. A Parr apparatus was used for low pressure hydrogenations. Plates used for radial centrifugal chromatography ("Chromatatron," Harrison Research, Palo Alto, CA) were prepared from Silica Gel 60 PF2-54 containing gypsum. All reactions were performed under an inert atmosphere of nitrogen or argon. Dry THF was obtained from a continuous still in our laboratory.

2-Benzyloxybenzaldehydes

General Procedure. Benzyl chloride (0.011 mole) was added dropwise into a reaction flask containing the appropriate salicylaldehyde (0.010 mol) and potassium carbonate (0.016 mol) in *N,N*-dimethylformamide (5 mL). After reflux for 2.5 hours, the reaction mixture was poured into 50 mL cold water and extracted with ether (3 x 30 mL). The organic extract was washed with 10% aqueous sodium hydroxide and brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with methylene chloride as the eluent to afford the respective 2-benzyloxybenzaldehydes.

2-Benzyloxy-4-fluorobenzaldehyde, 26. This compound was obtained as a solid in 91% yield from 4-flourosalicylaldehyde (**25**)[71]: mp 31 ^{o}C; ^{1}H NMR δ 10.41 (s, 1, CHO), 8.06 (t, 1, ArH, J = 8.1 Hz), 7.39 (m, 5, benzyl-ArH), 6,73 (m, 2, ArH), 5.15 (s, 2, CH_2); CIMS 231 (MH^+); Anal. ($C_{14}H_{11}FO_2$) C, H.

2-Benzyloxy-5-fluorobenzaldehyde, 36. This compound was obtained as a solid in 91% yield from 5-fluorosalicylaldehyde (**35**)[71]: mp 46 ^{o}C; ^{1}H NMR δ 10.51 (s, 1, CHO), 7.55 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 7.42 (m, 5, benzyl-ArH), 7.26 (m, 1, ArH), 7.05 (dd, 1, ArH, J = 3.0 and 9.0 Hz, 5.27 (s, 2, CH_2); CIMS 231 (MH^+); Anal. ($C_{14}H_{11}FO_2$) C, H.

Methyl indole-2-carboxylates

General Procedure.[66,68] Dry methanol[116] (85 mL) and sodium (0.19 mol) were added to a three neck flask equipped with mechanical stirrer, dropping funnel, low temperature thermometer, and nitrogen line. The resulting solution was cooled in a dry ice/CH_3CN bath to -20 °C. A solution of the appropriate benzaldehyde (0.041 mol) and methyl azidoacetate (0.19 mol) in dry methanol (42 mL) was added dropwise over 30 min. The mixture was allowed to stir for an additional 2-3 h at -8 °C. The heterogeneous mixture was then poured over ice, allowed to warm to 5-10 °C, filtered, and the precipitate washed on the funnel with water. The yellow solid was dried briefly on the filtration funnel with suction and collected to provide the azidocinnamate. The solid was dissolved in xylenes (200 mL) and the solution was washed twice with brine, followed by drying with $MgSO_4$. The resulting solution was added dropwise to a flask of xylenes at reflux (450 mL) and allowed to reflux until TLC indicated the reaction was complete. The mixture was cooled in a ice/NaCl bath and the resulting precipitate was removed by filtration to afford the respective methyl indole-2-carboxylate.

Methyl 6-fluoro-indole-2-carboxylate, 18. This compound was obtained as a white solid in 48% yield from 4-fluorobenzaldehyde: mp 158-159 °C; ^{1}H NMR δ 8.96 (br s, 1 NH), 7.64 (m, 1, ArH-5), 7.23 (s, 1, ArH-3), 7.10 (d, 1, ArH-4, J = 9.4 Hz), 6.95 (t, 1, ArH-7, J= 8.5 Hz), 3.98 (s, 3, $COOCH_3$); CIMS 194 (MH^+).

4-Benzyloxy-6-fluoro-indole-2-carboxylate, 28. This compound was obtained as a white solid in 54% yield from 2-benzyloxy-4-fluorobenzaldehyde: mp 228-229 ^{o}C; ^{1}H NMR (DMSO-d_6) δ 12.04 (br s, 1, NH), 7.42 (m, 5, benzyl-ArH), 7.12 (s, 1, ArH-3), 6.74 (d, 1, ArH, J = 9.0 Hz), 6.61 (d, 1, ArH, J = 9.0 Hz), 5.24 (s, 2, CH_2), 3.81 (s, 3, $COOCH_3$); CIMS 300 (MH^+); Anal. ($C_{17}H_{14}FNO_3$) C, H, N.

4-Benzyloxy-7-fluoro-indole-2-carboxylate, 38. This compound was obtained as a white solid in 43% yield from 2-benzyloxy-5-fluorobenzaldehyde: mp 179 ^{o}C; ^{1}H NMR (DMSO-d_6) δ 12.48 (br s, 1, NH), 7.42 (m, 5, benzyl-ArH), 7.19 (d, 1, ArH, J = 3.0 Hz), 6.99 (dd, 1, ArH, J = 6.0 and 12 Hz), 6.54 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 5.20 (s, 2, CH_2), 3.75 (s, 3, $COOCH_3$); CIMS 300 (MH^+); Anal. ($C_{17}H_{14}FNO_3$) C, H, N.

Indole-2-carboxylic acids

General Procedure. The appropriate indole-2-carboxylate (4.87 mmol) was added to a solution of aqueous NaOH (2N, 100 mL). The suspension that resulted was heated at 80-90 ^{o}C until homogenous, after which the solution was heated at reflux 1-2 h. The solution was cooled and acidified with aqueous 3N HCl, the resulting precipitate removed by filtration, washed on the filter with water and dried under vacuum to provide the indole-2-carboxylic acid.

6-Fluoro-indole-2-carboxylic acid, 19. This compound was obtained in 88% yield as a white solid: mp 244 °C (Lit.[117] mp 246 ° C); ^{1}H NMR (DMSO-d_6) δ 12.10 (br s, 1, COOH), 10.98 (br s, 1, NH), 6.81 (dd, 1, ArH), J = 5.6 and 8.9 Hz), 6.28 (m, 2, ArH), 6.09 (td, 1, ArH, J = 9.6 and 1.8 Hz); CIMS 179 (MH^+).

4-Benzyloxy-6-fluoroindole-2-carboxylic acid, 29. This compound was obtained in 97% yield as a white solid: mp 218-220 °C (dec); ^{1}H NMR (DMSO-d_6) δ12.88 (br s, 1, COOH), 11.87 (br s, 1, NH), 7.40 (m, 5, benzyl-ArH), 7.24 (s, 1, ArH-3), 6.73 (d, 1, ArH, J = 9.0 Hz), 6.58 (d, 1, ArH, J = 12 Hz), 5.24 (s, 2, CH_2); CIMS 286 (MH^+); Anal. ($C_{16}H_{12}FNO_3$) C, H, N.

4-Benzyloxy-7-fluoroindole-2-carboxylic acid, 39. This compound was obained in 94% yield as a white solid: mp 193 °C; ^{1}H NMR (DMSO-d_6) δ 13.02 (br s, 1, COOH), 12.28 (br s, 1, NH), 7.41 (m, 5, benzyl-ArH), 7.12 (t, 1, ArH, J = 3.0 Hz), 6.95 (dd, 1, ArH, J = 12 and 12 Hz), 6.52 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 5.20 (s, 2, CH_2); CIMS 286 (MH^+); Anal. ($C_{16}H_{12}FNO_3$) C, H, N.

Fluorinated indoles

General Procedure. The appropriate indole-2-carboxylic acid (40.5 mmol), copper powder (4 eq.) and *N*-methylpyrrolidinone (500 mL) were heated to reflux (240-250 °C). A continuous stream of nitrogen or argon was bubbled through the reaction mixture via a

metal tube, while maintaining reflux for 6 h. The mixture was cooled, filtered through Celite, and the filter cake washed with ether. The filtrate and ether washings were combined, diluted with water (1.8 L), and extracted four times with ether. The organic extract was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel with CH_2Cl_2 as eluent to give the respective fluoroindole.

6-Fluoroindole, 20.[69] This compound was obtained in 89% yield as clear needles: mp 64.5 °C (lit.[69] mp 75-76°C); ^{1}H NMR δ 8.15 (br s, 1, NH), 7.55 (dd, 1, ArH, J = 5.5 and 9.2 Hz), 7.19 (t, 1, ArH, J = 2.8), 7.08 (dd 1, ArH, J = 9.2 and 2.8 Hz), 6.89 (td, 1, ArH, J = 2.8 and 5.5), 6.54 (d, 1, ArH, J = 2.8 Hz); CIMS 136 (MH^+).

4-Benzyloxy-6-fluoroindole, 30. This compound was obtained in 81% yield as a white solid: mp 83-84 °C; ^{1}H NMR δ 8.12 (br s, 1, NH), 7.42 (m, 5, benzyl-ArH), 7.08 (t, 1, ArH, J = 3.0 Hz), 6.73 (d, 1, ArH, J = 9.0 Hz), 6.68 (t, 1, ArH, J = 3.0 Hz), 6.41 (d, 1, ArH, J = 12 Hz), 5.20 (s, 2, CH_2); CIMS 242 (MH^+); Anal. ($C_{15}H_{12}FNO_3$) C, H, N.

4-Benzyloxy-7-fluoroindole, 40. This material was obtained in 83% yield as a white solid: mp 58 °C; ^{1}H NMR δ 8.30 (br s, 1, NH), 7.42 (m, 5, benzyl-ArH), 7.16 (t, 1, ArH, J = 2.0 Hz), 6.77 (m, 2, ArH), 6.43 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 5.20 (s, 2, CH_2); CIMS 242 (MH^+); Anal. ($C_{14}H_{12}FNO$) C, H, N.

N,N-Diethyl-6-fluoro-indol-3-ylglyoxalylamide

6-Fluoro-indol-3-ylglyoxalyl chloride, 21.[69] A solution of oxalyl chloride (1.6 mL, 18.4 mmol) in anhydrous ether (20 mL) was added dropwise at 0 °C over 15 min to a solution of 6-fluorindole (1.91 g, 14.1 mmol, **20**) in anhydrous ether (50 mL). After stirring at room temperature for 5 h, the reaction mixture was filtered and the precipitate washed on the filter with cold ether. The filtrate was concentrated to precipitate additional glyoxyl chloride, which was removed by filteration and washed with cold ether. The combined crude 6-fluoro-3-indoleglyoxyl chloride (**21**) was obtained as a orange solid (2.95 g) that was used in the next step without further purification.

***N,N*-Diethyl-6-fluoro-indol-3-ylglyoxalylamide, 22.**[69] A solution of diethylamine (2.60 mL, 24.9 mmol) in anhydrous ether (20 mL) was added dropwise to a suspension of crude 6-fluoro-3-indoleglyoxyl chloride (1.91 g, 14.1 mmol, **21**) in anhydrous ether (100 mL) in a three neck flask equipped with mechanical stirrer, condenser, and dropping funnel. The crude product was collected by flitration and was washed on the filter with water, and dried under vacuum to provide **22** as a white solid (2.06 g, 55.4%). An analytical sample was recrystallized from acetone to give clear crystals: mp 178 °C (lit.[69] mp 189 °C); ^{1}H NMR (d_6-acetone) δ 11.30 (br s, 1, NH, 8.23 (dd, ArH, J = 5.8 and 8.6 Hz), 8.07 (s, 1, ArH-2), 7.31 (dd, 1, ArH, J = 2.3 and 10 Hz), 7.09 (td, 1, ArH, J = 8.7 and 2.3 Hz), 3.50 (q, 2, CH_2, J = 7.8 Hz), 3.35 (q, 2, CH_2, J = 7.8 Hz), 1.21 (t, 3, CH_3, J = 7.8 Hz), 1.15 (t, 3, CH_3, J = 7.8 Hz); CIMS 263 (MH^+).

N,N-Dimethyl-indol-3-ylglyoxalylamides

General Procedure.[70] A solution of oxalyl chloride (18.4 mmol) in anhydrous ether (20 mL) was added dropwise at 0 °C over 15 min to a solution of the appropriate indole (14.1 mmol) in anhydrous ether (50 mL). The reaction solution was stirred at room temperature for 5 h. In the same reaction flask, fitted with a dry ice/acetone condenser, gas inlet, and mechanical stirrer, dimethylamine gas was bubbled in until the reaction mixture had turned from yellow to white (pH = 8-9 on moist pH paper). The solid that formed was filtered, washed with water, and recrystallized from acetone to provide the respective *N,N*-dimethyl-indol-3-ylglyoxalylamide.

***N,N*-Dimethyl-6-fluoro-indol-3-ylglyoxalylamide, 23.**[69] This compound was obtained in 54% yield from 6-fluoroindole (**20**) as colorless crystals: mp 217-218 °C (lit.[69] mp 230-231 °C); ^{1}H NMR (d_6-acetone) δ 11.30 (br s, 1, NH), 8.21 (dd, 1, ArH, J = 5.9 and 8.8 Hz), 7.11 (s, 1, ArH), 7.21 (dd, 1, ArH, J = 2.9 and 10 Hz), 7.09 (td, 1, ArH, J = 2.9 and 10 Hz), 3.02 (s, 3, CH_3), 3.01 (s, 3, CH_3); CIMS 235 (MH^+).

***N,N*-Dimethyl-4-benzyloxy-6-fluoro-indol-3-ylglyoxalylamide, 32.** This compound was obtained in 68% yield from 4-benzyloxy-6-fluoroindole (**30**) as colorless crystals: mp 222 °C; ^{1}H NMR (d_6-acetone) δ 12.75 (s, 1, NH), 8.03 (s, 1, ArH), 7.47 (m, 5, benzyl-ArH), 6.87 (d, 1, ArH, J = 9.0 Hz), 6.59 (d, 1, ArH, J = 12 Hz), 5.33 (s, 2, CH_2), 2.98 (s, 3, CH_3), 2,93 (s, 3, CH_3); CIMS 341 (MH^+). Anal. ($C_{19}H_{17}FN_2O_3$) C, H, N.

***N,N*-Dimethyl-4-benzyloxy-7-fluoro-indol-3-ylglyoxalylamide, 42.** This compound was obtained in 38% yield from 4-benzyloxy-7-fluoroindole (**40**) as colorless crystals: mp 211 °C; ^{1}H NMR (DMSO-d_6) δ 12.80 (br s, 1, NH), 8.09 (s, 1, ArH-2), 7.42 (m, 5, benzyl-ArH), 6.96 (t, 1, ArH, J = 9.0 Hz), 6.58 (dd, 1, ArH, J = 3.3 and 9.0 Hz), 5.22 (s, 2, CH_2), 2.90 (s, 3, CH_3), 2.86 (s, 3, CH_3); CIMS 341 (MH^+); Anal. ($C_{19}H_{17}FN_2O_3$) C, H, N.

N,N-Dialkyltryptamines

General Procedure. A solution of the appropriate *N,N*-dialkyl-3-indoleglyoxylamide in dry THF was added dropwise into a slurry of lithium aluminum hydride (5 eq.) in dry THF at reflux. The mixture was held at reflux for 6-51 h until TLC indicated the reaction was complete. The reaction was then quenched with water, filtered through Celite, and the filtrate concentrated under reduced pressure. The residue was taken up in ether, washed with aqueous 1 N NaOH and brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified either by sublimation or recrystallization from ethyl acetate.

6-Fluoro-*N,N*-diethyltryptamine, 1.[43,69] The reflux time was 6 h. This amine was obtained in 67% yield as a white solid (sublimation): mp 59-60 °C (Lit.[43] mp 69-70 °C); ^{1}H NMR δ 8.02 (br s 1, NH), 7.51 (dd, 1, ArH, J = 5.5 and 8.8 Hz), 7.04 (dd, 1, ArH, J =

2.2 and 9.9), 7.01 (d, 1, ArH, J = 2.2, 6.89 (td, 1, ArH, J = 2.2 and 9.9 Hz), 2.91 (m, 2, CH_2), 2.79 (m, 2, CH_2), 2.67 (q, 2, CH_2, J = 6.9), 1.10 (t, 3, CH_3, J = 7.5 Hz); CIMS 235 (MH^+). The fumarate salt was prepared (EtOH/EtOAc): mp 134 °C; ^{1}H NMR (DMSO-d_6) δ10.98 (s, 1, NH), 7.54 (dd, ArH, J = 6.0 and 9.0 Hz), 7.21 (d, 1, ArH J = 3.0 Hz), 7.10 (dd, ArH, J = 3.0 and 9.0 Hz), 6.84 (td, 1, ArH, J = 3.0 and 12 Hz), 6.51 (s, 2, fumarate-H), 2,93 (m, 8, CH_2) 1.11(t, 6, CH_3, J = 9.0 Hz); CIMS 235 (MH^+); Anal. ($C_{18}H_{23}FN_2O_4$) C, H, N.

6-Fluoro-*N,N*-dimethyltryptamine, 2.[69] The reflux time was 9.5 h. This amine was obtained in 80% yield as a white solid (sublimation): mp 95.5-96.5 °C (lit.[69] mp 101-102); ^{1}H NMR δ 8.10 (br s, 1, NH), 7.47 (dd, 1, ArH, J = 5.0 and 9.4 Hz), 7.02 (dd, 1, ArH, J = 2.4 and 9.4 Hz), 6.99 (d, 1, ArH, J = 2.4 Hz), 6.89 (td, 1, ArH, J = 2.4 and 9.4), 2.93 (t, 2, CH_2, J = 10 Hz), 2.65 (t, 2, CH_2, J = 10 Hz), 2.35 (s, 3, CH_3); CIMS 207 (MH^+). The fumarate salt was prepared (EtOH/EtOAc): mp 174 °C; ^{1}H NMR (DMSO-d_6) δ 10.96 (s, 1, NH), 7.54 (dd, 1, ArH, J = 3.0 and 6.0 Hz), 7.18 (d, 1, ArH, J = 3.0 Hz), 7.10 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 6.83 (td, 1, ArH, J = 3.0 and 9.0 Hz), 6.52 (s, 2, fumarate), 2.93 (s, 4, CH_2), 2.60 (s, 6, CH_3); CIMS 207 (MH^+); Anal. ($C_{16}H_{19}FN_2O_4$) C, H, N.

4-Benzyloxy-6-fluoro-*N,N*-dimethyltryptamine, 33. The reflux time was 49 h. This tryptamine was obtained in 87% yield as a white solid (recrystallized from EtOAc): mp 131 °C; ^{1}H NMR (CD_3OD) δ 7.41 (m, 5, benzyl-ArH), 6.87 (s, 1, ArH-2), 6.63 (dd, 1,

ArH-5, J = 2.1 and 9.0 Hz), 6.39 (dd, 1, ArH-7, J = 3.0 and 12 Hz), 3.10 (s, 2, CH_2), 2.95 (m, 2, CH_2), 2.60 (m, 2, CH_2), 2.10 (s, 6, CH_3); CIMS 313 (MH^+); Anal. ($C_{19}H_{21}FN_2O$) C, H, N.

4-Benzyloxy-7-fluoro-*N,N*-dimethyltryptamine, 43. The reflux time was 51 h. This tryptamine was obtained in 88% yield as a white solid (recrystallized from EtOAc): mp 155 °C; ^{1}H NMR δ 8.25 (br s, 1, NH), 7.39 (m, 5, benzyl-ArH), 6.92 (d, 1, ArH-2, J = 1.7 Hz), 6.72 (dd, 1, ArH, J = 9.0 and 11 Hz), 6.36 (dd, 1, ArH, J = 8.5 and 3.1 Hz), 5.15 (s, 2, CH_2), 3.03 (t, 2, CH_2, J = 7.5 Hz), 2.58 (t, 2, CH_2, J = 7.6 Hz), 2.15 (s, 6, CH_3); CIMS 313 (MH^+); Anal. ($C_{19}H_{21}FN_2O$) C, H, N.

Fluorinated Analogs of Psilocin

General Procedure. The appropriate benzyloxytryptamine (3.20 mmol) was hydrogenated at 50 psig in 95% EtOH (250 mL) over 10% Pd/C (340 mg) for 4 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a solid which was purified by sublimation to afford the respective hydroxytryptamine.

6-Fluoro-4-hydroxy-*N,N*-dimethyltryptamine, (6-Fluoropsilocin), 8. This compound was obtained in quantitative yield as a white solid: mp 178 °C (dec); ^{1}H NMR (CD_3OD) δ 6.83 (s, 1, ArH), 6.46 (dd, 1, ArH, J = 3.0 and 9.0 Hz), 6.10 (dd, 1, ArH, J = 3.0 and 12 Hz), 2.98 (t, 2, CH_2, J = 6.0 Hz), 2.75 (t, 2, CH_2, J = 6.0 Hz), 2.37 (s, 6, CH_3); CIMS 223 (MH^+); Anal. ($C_{12}H_{15}FN_2O$) C, H, N. The fumarate salt was prepared (2:1 base:acid)

and recrystallized (EtOH/EtOAc): mp 226 °C (dec); ^{1}H NMR (DMSO-d_6) δ 10.69 (br s, 2, NH), 6.92 (d, 2, ArH, J = 2.0 Hz), 6.49 (dd, 2, ArH, J = 2.0 and 10 Hz), 6.50 (s, 2, fumarate-H), 6.13 (dd, 2, ArH, J = 3.0 and 12 Hz), 2.89 (t, 4, CH_2, J = 6.0 Hz), 2.70 (t, 4, CH_2, J = 6.0 Hz), 2.34 (s, 12, CH_3); CIMS 223 (MH^+); Anal. ($C_{28}H_{34}F_2N_4O_6$) C, H, N.

7-Fluoro-4-hydroxy-*N*,*N*-dimethyltryptamine, (7-Fluoropsilocin), 9. This compound was obtained in 98% yield as a white solid: mp 170 °C (dec); ^{1}H NMR δ 8.03 (br s, 1, NH), 6.88 (d, 1, ArH-2, J = 2.0 Hz), 6.75 (dd, 1, ArH, J = 8.4 and 10 Hz), 6.40 (dd, 1, ArH, J = 3.7 and 8.5 Hz), 2.94 (m, 2, CH_2), 2.69 (m, 2, CH_2), 2.38 (s, 6, CH_3); CIMS 223 (MH^+); Anal. ($C_{12}H_{15}FN_2O$) C, H, N. The fumarate salt was prepared (2:1 base:acid) and recrystallized (EtOH/EtOAc): mp 220 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.09 (br s, 2, NH), 7.02 (d, 2, ArH, J = 1.9 Hz), 6.62 (dd, 2, ArH, J = 8.3 and 11 Hz), 6.49 (s, 2, fumarate-H), 6.16 (dd, 2, ArH, J = 3.4 and 8.0 Hz), 1.85 (t, 4, CH_2, J = 7.0 Hz), 2.75 (t, 4, CH_2, J = 7.0 Hz), 2.37 (s, 12, CH_3); CIMS 223 (MH^+); Anal. ($C_{28}H_{34}F_2N_4O_6$) C, H, N.

Fluorinated analogs of 5-methoxy-DMT

2-Fluorophenol, 49.[73] A solution of 2-fluoroaniline (7.00 g, 63.0 mmol) in 52 mL of 6M H_2SO_4 was cooled in an salt/ice bath to -5 °C and a solution of sodium nitrite (4.65 g, 67.4 mmol) in water (7.5 mL) was added dropwise with stirring, while maintaining the temperature between -5 and 5 °C. The reaction mixture was allowed to warm to room

temperature and the excess nitrite was decomposed with urea (250 mg). This solution of the diazonium salt was then added dropwise to a heated (150 °C) mixture of $CuSO_4 \cdot 5H_2O$ (28.30 g, 113 mmol), water (63 mL), and 96% H_2SO_4 in a flask fitted for steam distillation apparatus. A slow current of steam was passed through the system to remove the phenol as it formed. The distillate was extracted with ether and the ether extract washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude phenol was purified by column chromatography over silica gel with CH_2Cl_2 as eluent to yield pure **49** (3.41 g, 48%) as a yellow oil: ^{1}H NMR δ 7.07 (m, 3, ArH), 6,89 (m, 1, ArH), 5.29 (s, 1, OH); CIMS 113 (MH^+).

2-Fluoroanisole, 50.[73] A suspension of 2-fluorophenol (17.2 g, 153 mmol, **49**), potassium carbonate (42.0 g, 304 mmol), and dimethylsulfate (21.9 mL, 231 mmol) in absolute ethanol (578 mL) was heated at reflux for 8 h. After cooling, the mixture was poured into water (1000 mL) and extracted with CH_2Cl_2 (3 x 800 mL). The organic extract was washed with 2 N NaOH (3 x 500 mL), water (2 x 500 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel with CH_2Cl_2 as eluent to yield pure **50** (17.7 g, 92%) as a yellow liquid: ^{1}H NMR δ 7.01 (m, 4, ArH), 7.13-6.80 (m, 4, Ar-H), 3.91 (s, 3, OCH_3). CIMS 127 (MH^+).

2-Fluoro-4-nitroanisole, 51. Nitric acid (2.6 mL) was added to a stirred mixture of 2-fluoroanisole (5.01 g, 39.7 mmol, **50**), sulfuric acid (96%, 675 mL) and water (250 mL) at 0 °C. A solution of sodium nitrite (2.71 g, 39.3 mmol) in water (50 mL) was added

dropwise. The reaction mixture was warmed to room temperature and stirred for 3 h, then diluted with 3000 mL of water and placed in the refrigerator overnight. The precipitate that formed (containing the ortho-nitrated product **52** in less than 1% yield as detected by ^{1}H NMR) was collected by filtration and purified by column chromatography over silica gel with CH_2Cl_2 as eluent to obtain pure **51** in 66% yield (4.08 g) as a white solid: mp 95-96 °C (Aldrich mp 104 °C); ^{1}H NMR δ 8.08 (m, 1, ArH), 7.99 (dd, 1, ArH, J = 11 and 2.7 Hz), 7.04 (t, 1, ArH, J = 8.6 Hz), 4.01 (s, 3, OCH_3); CIMS 172 (MH^+)

2-Fluoro-4-aminoanisole, 53. A solution of 2-fluoro-4-nitroanisole (9.20 g, 53.8 mmol, **51**) in 95% ethanol (200 mL) was hydrogenated at 45 psig for 16 h over 10% Pd/C (1.50 g). The catalyst was removed by filtration, washed with ethanol, and the filtrate was evaporated under reduced pressure to provide **53** (7.52 g, 99%) as a solid: mp 75 °C (Aldrich mp 81-83 °C); ^{1}H NMR δ 6.80 (t, 1, ArH, J = 9.0 Hz), 6.49 (dd, 1, ArH, J = 13 and 2.6 Hz), 6.39 (m, 1, ArH), 3.82 (s, 3, OCH_3), 3.50 (br s, 2, NH_2); CIMS 142 (MH^+).

3-Fluoro-4-methoxyphenylhydrazine hydrochloride, 55. A solution of sodium nitrite (2.58 g, 37.4 mmol) in water (8 mL) was added dropwise to a solution of 2-fluoro-4-aminoanisole (**53**) (5.28 g, 37.4 mmol) in aqueous 2.35 M HCl at 0 °C. The solution was stirred for 10 min and then slowly added dropwise to a rapidly stirred mixture of $SnCl_2 \cdot 2H_2O$ (33.74 g, 149.5 mmol) in concentrated HCl (140 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 15 minutes, and filtered. The collected precipitate was washed on the filter with several large portions of ether and

dried under vacuum to give **55** (4.73 g, 66%), which was used in the next step without further purification: mp > 100°C (dec); ^{1}H NMR (DMSO-d_6) δ 10.20 (br s, 3, NH_3^+), 8.15 (br s, 1, NH), 7.10 (t, 1, ArH, J = 9.2 Hz), 6.97 (dd, 1, ArH, J = 13 and 2.6 Hz), 6.97 (m, 1, ArH), 3.80 (s, 3, OCH_3).

6-Fluoro- and 4-fluoro-5-methoxy-*N,N*-dimethyltryptamine, 10 and 11. 4-(*N,N*-Dimethylamino)butanal dimethylacetal[72] (710 mg, 4.40 mmol, **47**) was added to a heated (80 °C) solution of hydrazine **55** (530 mg, 2.75 mmol) in 24% aqueous acetic acid (40 mL) and the reaction was stirred at 85 °C for 27.5 h. After cooling, the solution was basified to pH 10-11 with concentrated ammonium hydroxide and then extracted with ether (3 x 30 mL). The organic extract was dried (Na_2SO_4), evaporated under reduced pressure, and the residue was purified by centrifugal radial chromatography ("Chromatotron,", Harrison Research, Palo Alto, CA), on a 4 mm silica gel plate, eluting with 5% MeOH/CH_2Cl_2 under an atmosphere of nitrogen and ammonia to afford 6-fluoro-5-methoxy-*N,N*-dimethyltryptamine (318 mg, 49%, **10**): mp 73 °C; ^{1}H NMR δ 7.99 (br s, 1, NH), 7.09 (m, 2, ArH), 6.98 (s, 1, ArH), 3.93 (s, 3, OCH_3), 2.90 (t, 2, CH_2), J = 9.0 Hz), 2.62 (t, 2, CH_2, J = 9.0 Hz), 2.38 (s, 6, NCH_3); CIMS 237 (MH^+); Anal. ($C_{13}H_{17}FN_2O$) C, H, N; prepared as the fumarate salt (2:1 base:acid) and recrystallized (EtOH/EtOAc): mp 208 °C; ^{1}H NMR (DMSO-d_6) δ 10.73 (br s, 2, NH), 7.15 (m, 6, ArH), 6.50 (s, 2, fumarate-H), 3.83 (s, 6, OCH_3), 2.85 (m, 4, CH_2), 2.75 (m, 4, CH_2), 2.40 (s, 12, NCH_3); CIMS 237 (MH^+); Anal. ($C_{30}H_{38}F_2N_4O_6$) C, H, N.

Continued elution afforded 4-fluoro-5-methoxy-*N,N*-dimethyltryptamine (45 mg, 7.0%, **11**): mp 75 °C; ^{1}H NMR δ 7.94 (br s, 1, NH), 6.96 (m, 3, ArH), 3.93 (s, 3, OCH_3), 3.02 (t, 2, CH_2, J = 9.0 Hz, 2.67 (t, 2, CH_2, J = 9.0 Hz), 2.37 (s, 6, NCH_3); prepared as the fumarate salt (2:1 base:acid): mp 185 °C; ^{1}H NMR (DMSO-d_6) δ 10.89 (br s, 2, NH), 7.13 (d, 2, ArH, J = 2.1 Hz), 7.06 (d, 2, ArH, J = 8.7 Hz), 6.93 (t, 2, ArH, J = 8.4 Hz), 6.50 (s, 2, fumarate-H) 3.80 (s, 6, OCH_3), 2.90 (t, 4, CH_2, J = 7.8 Hz), 2.65 (t, 4, CH_2, J = 7.8 Hz), 2.30 (s, 12, NCH_3); CIMS 237 (MH^+); Anal. ($C_{30}H_{38}F_2N_4O_6$) C, H, N.

4,5-Difluoro- and 5,6-difluoro-*N,N*-dimethyltryptamine, 5 and 6

3,4-Difluorophenylhydrazine hydrochloride, 59. This compound was obtained from 3,4-difluoroaniline in 81% yield following the same procedure used to prepare hydrazine **55**, and was used without further purification in the next step: mp >100° C (dec); ^{1}H NMR (DMSO-d_6) δ 10.38 (s, 3, NH_3^+), 8.50 (br s, 1, NH), 7.35 (q, 1, ArH, J = 9.5 Hz), 7.09 (m, 1, ArH), 6.81 (d, 1, ArH, J = 8.7 Hz).

5,6-Difluoro- and 4,5-difluoro-*N,N*-dimethyltryptamine, 6 and 5. Hydrazine **59** (4.60 g, 25.5 mmol) was dissolved in 25% aqueous acetic acid (350 mL) containing concentrated sulfuric acid (6 mL) and the mixture was heated to 80-85 °C. Next, 4-(*N,N*-Dimethylamino)butanal dimethylacetal[72] (4.93 g, 30.6 mmol, **47**) was added to the hydrazine solution and the mixture was heated at 85 °C for 22 h. After cooling, the solution was basified to pH 10-11 with concentrated ammonium hydroxide and extracted

with 3 x 250 mL ether. The ether extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by centrifugal radial chromatography ("Chromatotron,", Harrison Research, Palo Alto, CA), in two portions on 4 mm silica gel plates, eluting with 5% MeOH/CH_2Cl_2 under an atmosphere of nitrogen and ammonia to afford **6** (2.43 g, 43%): mp 114 °C; ^{1}H NMR δ 8.23 (br s, 1, NH), 7.32 (m, 1, ArH), 7.09 (dd, 1, ArH, J = 11 and 6.7 Hz), 7.03 (s, 1, ArH), 2.89 (t, 2, CH_2, J = 7.8 Hz), 2.63 (t, 2, CH_2, J = 7.8 Hz), 2.36 (s, 6, NCH_3); CIMS 225 (MH^+); Anal. ($C_{12}H_{14}F_2N_2$) C, H, N; prepared as the benzoate salt (recrystallized from ether/CH_2Cl_2): mp 122 °C; ^{1}H NMR (DMSO-d_6) δ 11.00 (br s, 1, NH), 7.94 (m, 2, benzoate-H), 7.50 (m, 4, ArH and benzoate-H), 7.31 (dd, 1, ArH, J = 11 and 7.0 Hz), 7.22 (s, 1, ArH), 2.82 (t, 2, CH_2, J = 7.7 Hz), 2.63 (t, 2, CH_2, J = 7.7 Hz), 2.32 (s, 6, NCH_3); CIMS 225 (MH^+); Anal. ($C_{19}H_{20}F_2N_2O_2$) C, H, N.

Further elution afforded **5** (1.22 g, 21%): mp 94 °C; ^{1}H NMR δ 8.26 (br s, 1, NH), 6.97 (m, 3, ArH), 3.03 (t, 2, CH_2, J = 7.7 Hz), 2.67 (t, 2, CH_2, J = 7.7 Hz), 2.36 (s, 6, NCH_3); CIMS 225 (MH^+); Anal. ($C_{12}H_{14}F_2N_2$) C, H, N; prepared as the fumarate salt (recrystallized from EtOH/EtOAc): mp 158 °C; ^{1}H NMR (DMSO-d_6) δ 11.25 (br s, 1, NH), 7.28 (s, 1, ArH), 7.08 (m, 2, ArH, 6.53 (s, 2, fumarate-H), 2.99 (t, 2, CH_2, J = 7.7 Hz), 2.82 (t, 2, CH_2, J = 7.7 Hz), 2.45 (s, 6, NCH_3); CIMS 225 (MH^+) Anal. ($C_{16}H_{18}F_2N_2O_4$) C, H, N.

Fischer indole cyclizations in 4% H_2SO_4

6-Fluoro- and 4-fluoro-*N,N*-dimethyltryptamine, 2 and 3. Following the general procedure of Chen *et al.*,[72] an aqueous 4% sulfuric acid solution was heated to 50 °C over 30 minutes while bubbling nitrogen gas through the solution to removed dissolved gases. To this was added 3-fluorophenylhydrazine hydrochloride (4.40 g, 27.1 mmol) with stirring. 4-(*N,N*-dimethylamino)butanal dimethylacetal[72] (5.24 g, 32.5 mmol) was added dropwise and the solution was heated at reflux for 2.5 hours. After cooling, 30% aqueous NH_4OH was slowly added, maintaining the temperature between 25-30 °C, to reach pH 8-9. The mixture was then extracted with CH_2Cl_2, the extract was dried with $MgSO_4$, and evaporated under reduced pressure. The residue was purified by centrifugal radial chromatography ("Chromatotron,", Harrison Research, Palo Alto, CA), in two portions on 4 mm silica gel plates, eluting with 5% MeOH/CH_2Cl_2 under an atmosphere of nitrogen and ammonia to afford **2** (1.79 g, 32%): mp 95-96 °C (see experimental for **2** under "*N,N*-dialkyltryptamines"); and **3** (893 mg, 16%) as a white solid: mp 89.5 °C (lit.[78] mp 100-101 °C); ^{1}H NMR δ 8.15 (br s, 1, NH), 7.07 (m, 2, ArH), 6.97 (s, 1, ArH), 6.73 (m, 1, ArH), 3.03 (t, 2, CH_2, J = 7.9 Hz), 2.65 (t, 2, CH_2, J = 7.9 Hz), 2.34 (s, 6, NCH_3); CIMS 207 (MH^+); Anal. ($C_{12}H_{15}FN_2$) C, H, N; prepared as the fumarate salt (recrystallized from EtOH/EtOAc): mp 159 °C; ^{1}H NMR (DMSO-d_6) δ 11.15 (br s, 1, NH), 7.17 (m, 2, ArH), 7.01 (td, 1, ArH, J = 8.0 and 5.2 Hz), 6.70 (dd, 1, ArH, J = 12 and 7.8 Hz), 6.53 (s, 2, fumarate-H), 3.00 (m, 2, CH_2), 2.87 (m, 2, CH_2), 2.48, s, 6, NCH_3); CIMS 207 (MH^+); Anal. ($C_{16}H_{19}FN_2O_4$) C, H, N.

5-Fluoro-*N,N*-dimethyltryptamine, 4.[72] This compound was synthesized as reported previously[72] and prepared as the benzoate salt (recrystallized from EtOAc): mp 130 °C; ^{1}H NMR (DMSO-d_6) δ 10.90 (br s, 1, NH), 7.93 (m, 2, benzoate-H), 7.57 (m, 1, benzoate-H), 7.46 (m, 2, benzoate-H), 7.29 (m, 2, ArH), 7.23 (d, 1, ArH, J = 2.1 Hz), 6.88 (td, 1, ArH, J = 9.2 and 2.6 Hz), 2.81 (t, 2, CH_2, J = 7.8 Hz), 2.60 (t, 2, CH_2, J = 7.8 Hz), 2.30 (s, 6, NCH_3); CIMS 207 (MH^+); Anal. ($C_{19}H_{21}FN_2O_2$) C, H, N.

4,7-Difluoro-*N,N*-dimethyltryptamine, 7. This compound was prepared from 2,5-difluorophenylhydrazine hydrochloride by the same procedure used for the synthesis of **3**. The product was purified by chromatography with difficulty to obtain a 15% yield of a dark oil: ^{1}H NMR δ 8.68 (br s, 1, NH), 6.96 (s, 1, ArH), 6.70 (m, 1, ArH), 6.59 (m, 1, ArH), 3.02 (t, 2, CH_2, J = 7.6 Hz), 2.68 (t, 2, CH_2, J = 7.6 Hz), 2.36 (s, 6, NCH_2); CIMS 225 (MH^+); prepared as the fumarate salt (2:1 base:acid) recrystallized from EtOH/EtOAc: mp 189 °C; ^{1}H NMR (DMSO-d_6) δ 11.55 (br s, 2, NH), 7.25 (d, 2, ArH, J = 2.1 Hz), 6.84 (m, 2, ArH), 6.66 (m, 2, ArH), 6.51 (s, 2, fumarate-H), 2.92 (t, 4, CH_2, J = 7.8 Hz), 2.66 (t, 4, CH_2, J = 7.8 Hz), 2.32 (s, 12, NCH_3); CIMS 225 (MH^+); Anal. ($C_{28}H_{32}F_4N_4O_4$) C, H, N.

Thienopyrroles

***N*-*t*-Butoxycarbonyl-*N*-(2-thienyl)hydrazine, 68.**[84] A mixture of 2-*t*-butoxycarbonyl-aminothiophene[88] (20.23 g, 101.6 mmol, **67**) and NaH (2.55 g, 106.3 mmol) was stirred in anhydrous DMF (192 mL) for 30 min at 50-60 ^{o}C. After cooling to 10 ^{o}C, a suspension of *O*-diphenylphosphinyl-hydroxylamine[98] (28.41 g, 121.8 mmol, **64**) in anhydrous DMF was added dropwise. The reaction mixture was stirred for 13 h at room temperature and then poured into ice water (960 mL) and extracted with CH_2Cl_2 (3 x 500 mL). The organic extract was washed with water, brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel with CH_2Cl_2 as eluent to afford, after concentration, **68** (17.74 g, 81.6%): mp 35-36 ^{o}C (lit.[84] 40-41 ^{o}C); : ^{1}H NMR δ 6.89 (br s, 1, ArH), 6.83 (m, 2, ArH), 4.56 (br s, 2, NH_2), 1.57 (s, 9, *t*-butyl-H).

Ethyl-(6-(-*t*-butoxycarbonyl)-4-thieno[2,3-*b*]pyrrolyl) acetate, 85. Following the general procedure of Wensbo *et al.*[55], ethyl 4-bromocrotonate (0.227 mL, 1.6 mmol) was added in one portion with stirring to a mixture of 3-bromo-2-(*N*-*t*-butoxycarbonylamino)thiophene[118] (305.6 mg, 1.1 mmol, **83**) and finely ground potassium carbonate (607.3 mg, 4.4 mmol) in anhydrous DMF (4 mL). The reaction was stirred at room temperature for 24 h, after which another 0.5 equivalent (0.076 mL) of ethyl 4-bromocrotonate was added and the reaction mixture was stirred at room temperature for an additional 24 h. Triphenylphosphine (28.8 mg, 0.1 eq) and palladium(II)acetate (12.3

mg, 0.05 eq) were added and the reaction was stirred for 30 min at room temperature, after which the mixture was heated to 70-75 °C for 6 h. After cooling to room temperature 20 mL ether was added, and the mixture was washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel with CH_2Cl_2 as eluent. Solvent removal gave pure **85** as a white solid in 68% yield: mp 64 °C (lit.[55] mp 69-71 °C; ^{1}H NMR δ 7.34 (br s, 1, ArH), 6.99 (s, 2, ArH), 4.18 (q, 2, CH_2CH_3, J = 7.1 Hz), 3.63 (s, 2, CH_2), 1.64 (s, 9, *t*-butyl-H), 1.27 (t, 3, CH_2CH_3, J = 7.1 Hz); CIMS 310 (MH^+); Anal. ($C_{15}H_{19}NO_4S$) C, H, N.

***N,N*-dimethyl-4*H*-thieno[3,2-*b*]pyrrole-6-acetamide, 79.** Methyl chloroaluminum dimethylamide[103] (50.8 mL, 0.67M solution in benzene/toluene, **78**) was added in one portion to a solution of ethyl (4*H*-thieno[3,2-*b*]pyrrolyl)-6-acetate[55] (3.56 g, 17.0 mmol, **77**) in dry benzene (178 mL). The solution was allowed to reflux for 2 h, was cooled to room temperature, and then carefully quenched with water (CAUTION: vigorous gas evolution!). The organic layer was separated and the aqueous layer was extracted three times with 150 mL ethyl acetate. The organic extracts were combined, dried with $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel with 50% EtOAc/CH_2Cl_2 as eluent to afford after solvent removal amide **79** (3.35 g, 95%): mp 128 °C, ^{1}H NMR δ mp 128 °C; ^{1}H NMR δ 8.36 (br s, 1, NH), 7.08 (d, 1, ArH, J = 5.0 Hz), 6.91 (d, 1, ArH, J = 5.1 Hz), 6.88 (s, 1, ArH),

3.71 (s, 2, CH_2), 3.07 (s, 3, NCH_3), 3.00 (s, 3, NCH_3); CIMS 209 (MH^+); Anal. ($C_{10}H_{12}N_2OS$) C, H, N.

***N,N*-dimethyl-6*H*-thieno[2,3-*b*]pyrrole-4-acetamide, 87.** This amide was obtained from (6*H*-thieno[2,3-*b*]pyrrolyl)-4-acetate[55] and methylchloroaluminum dimethylamide[103] by the same procedure used for the preparation of amide **79**. Reflux time was 20 minutes to afford **87** after isolation and purification in 89% yield: mp 107 °C; ^1H NMR δ 8.54 (br s, 1, NH), 7.00 (d, 1, ArH, J = 5.3 Hz), 6.82 (s,1, ArH), 6.80 (d, 1, ArH, J = 5.3 Hz), 3.72 (s, 2, CH_2), 3.04 (s, 3, NCH_3), 2.97 (s, 3, NCH_3); CIMS 209 (MH^+); Anal. ($C_{10}H_{12}N_2OS$) C, H, N.

***N,N*-Dimethyl-2-(4*H*-thieno[3,2-*b*]pyrrol-6-yl)ethanamine, 12.** The amide **79** (2.89 g, 13.9 mmol) in THF was added dropwise into a mixture of LAH (1.58 g, 41.6 mmol) in dry THF (330 mL). The reaction mixture was allowed to reflux for 2 h, then cooled to room temperature and quenched with water. The mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in 30 mL ether, dried with Na_2SO_4, concentrated under reduced pressure. The crude product was purified by centrifugal radial chromatography ("Chromatotron,", Harrison Research, Palo Alto, CA), in two portions on 4 mm silica gel plates, eluting with 5% MeOH/CH_2Cl_2 under an atmosphere of nitrogen and ammonia to afford **12** (2.61 g, 97%) as a off-white solid: mp 43-44 °C; ^1H NMR δ 8.31 (br s, 1, NH), 7.08 (d, 1, ArH, J = 5.2 Hz), 6.91 (d, 1, ArH, J = 5.2 Hz), 6.80 (s, 1, ArH), 2.83 (t, 2, CH_2, J = 8.3 Hz), 2.66 (t, 2, CH_2, J = 8.3

Hz), 2.33 (s, 6, NCH_3); CIMS 195 (MH^+); Anal. ($C_{10}H_{14}N_2S$) C, H, N; prepared as the benzoate salt (Recrystallized from EtOAc): mp 178°C; ^1H NMR (DMSO-d_6) δ 10.82 (br s, 1, NH), 7.95 (m, 2, benzoate-H), 7.56 (t, 1, benzoate-H, J = 7.5 Hz), 7.46 (t, 2, benzoate-H, J = 7.2 Hz), 7.12 (d, 1, ArH, J = 5.3 Hz), 6.94 (d, 1, ArH, J = 5.3 Hz), 6.86 (s, 1, ArH-5), 2.71 (t, 2, CH_2, J = 8.0 Hz), 2.60 (t, 2, CH_2, J = 8.0 Hz), 2.27 (s, 6, NCH_3); CIMS 195 (MH^+); Anal. ($C_{17}H_{20}N_2O_2S$) C, H, N.

***N,N*-Dimethyl-2-(6*H*-thieno[2,3-*b*]pyrrol-4-yl)ethanamine, 13.** This amine was obtained in 93% yield as a off-white solid by the same procedure used to prepare amine **12**,: mp 38-39 °C; ^1H NMR δ 8.28 (br s, 1, NH), 7.00 (d, 1, ArH J = 5.2 Hz), 6.82 (d, 1, ArH, J = 5.2 Hz), 6.81 (s, 1, ArH), 2.85 (t, 2, CH_2, J = 7.3 Hz), 2.62 (t, 2, CH_2, J = 7.1 Hz), 2.33 (s, 6, NCH_3); CIMS 195 (MH^+); Anal. ($C_{10}H_{14}N_2S$) C, H, N; prepared as the benzoate salt (recrystallized from EtOAc): mp 136 °C; ^1H NMR (DMSO-d_6) δ 10.95 (br s, 1, NH), 7.93 (d, 2, benzoate-H, J = 7.9 Hz), 7.56 (t, 1, benzoate-H, J = 7.2 Hz), 7.45 (t, 2, benzoate-H, J = 7.7 Hz), 6.97 (d, 1, ArH, J = 5.2 Hz), 6.86 (d, 1, ArH, J = 5.0 Hz), 6.83 (s, 1, ArH-5), 2.74 (m, 2, CH_2), 2.62 (m, 2, CH_2), 2.30 (s, 6, NCH_3); CIMS 195 (MH^+); Anal. ($C_{17}H_{20}N_2O_2S$) C, H, N.

Table 7. Elemental Analysis Data.

	%C	%C	%H	%H	%N	%N
	Calc'd	**Found**	**Calc'd**	**Found**	**Calc'd**	**Found**
1 • Fumarate	61.70	61.42	6.62	6.65	7.99	7.94
2 • Fumarate	59.62	59.59	5.94	5.96	8.69	8.70
3	69.88	69.53	7.33	7.42	13.58	13.49
3 • Fumarate	59.62	59.88	5.94	5.99	8.69	8.96
4 • Benzoate	69.49	69.30	6.45	6.46	8.53	8.46
5	64.27	63.99	6.29	6.26	12.49	12.26
5 • Fumarate	56.47	56.79	5.33	5.44	8.23	8.26
6	64.27	64.03	6.29	6.20	12.49	12.45
6 • Benzoate	65.88	65.77	5.82	5.75	8.09	8.00
7 • Fumarate	59.57	59.79	5.71	5.80	9.92	9.75
8	64.85	64.49	6.80	6.67	12.60	12.21
8 • Fumarate	59.99	59.75	6.11	6.16	9.99	10.27
9	64.85	64.94	6.80	9.96	12.60	12.50
9 • Fumarate	59.99	59.98	6.11	6.17	9.99	9.80
10	66.08	65.99	7.25	7.34	11.86	12.00
10 • Fumarate	61.21	60.96	6.51	6.44	9.52	9.43
11	66.08	65.73	7.25	7.30	11.86	11.61
11 • Fumarate	61.21	61.26	6.51	6.59	9.52	9.47
12	61.82	61.68	7.26	7.23	14.42	14.36
12 • Benzoate	64.53	64.35	6.37	6.28	8.85	8.65
13	61.82	61.66	7.26	7.30	14.42	14.38
13 • Benzoate	64.53	64.58	6.37	6.06	8.85	8.77
26	73.03	73.20	4.82	4.70	--	--
28	68.21	68.48	4.72	4.67	4.68	4.64
29	67.35	67.66	4.24	4.16	4.91	4.93
30	74.66	74.38	5.02	4.81	5.81	8.89
32	67.05	66.81	5.03	5.05	8.23	7.96
33	73.04	72.77	6.78	6.79	8.97	8.59

36	73.03	72.71	4.82	4.55	--	--
38	68.22	68.25	4.71	4.57	4.68	4.61
39	67.37	67.62	4.24	4.10	4.91	5.00
40	74.68	75.05	5.01	4.82	5.81	5.96
42	67.05	67.09	5.03	4.96	8.23	8.35
43	73.05	73.32	6.78	6.82	8.97	8.78
79	57.67	57.49	5.81	5.73	13.45	13.20
85	58.23	58.26	6.19	6.27	4.53	4.44
87	57.67	57.81	5.81	5.91	13.45	13.22

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VITA

The author was born in 1966 in Brainerd, Minnesota. He is the youngest in a family of eight children raised by the mother only. After graduating valedictorian of his senior class in Ada, Minnesota in 1984, he worked on a double major in college, finishing his bachelor of science degree in chemistry in 1991 at Moorhead State University, Moorhead, Minnesota, and completing his bachelor of science degree in Pharmacy in 1992 at neighboring North Dakota State University College of Pharmacy just across the Red River in Fargo, North Dakota. The author completed a six-month cooperative research position with American Crystal Sugar Research Center in 1986 and was awarded a Summer Research Fellowship at North Dakota State University, Department of Polymers and Coatings, in 1987. He was also a Ronald E. McNair Scholar his last three years of undergraduate education at NDSU.

After passing the national and state pharmacy board exams and state oral qualifying exams, he became a registered pharmacist in July, 1992. He was admitted to the Graduate School of Purdue University, West Lafayette, Indiana, in the Department of Medicinal Chemistry and Molecular Pharmacology in August 1992, and worked toward his Doctor of Philosophy degree under the direction of Dr. David E. Nichols in the research area of fluorinated and thienopyrrole analogs of hallucinogenic tryptamines and molecular recognition at serotonin receptors in the brain. He was also a teaching assistant for pharmacognosy laboratories and medicinal chemistry classes under the direction of Dr. James Robbers and Dr. Jerry McLaughlin for three years and was awarded the

Department of Medicinal Chemistry and Molecular Pharmacology's Kienly Award for Excellence in Teaching in 1995. He also was inducted into the Rho Chi Pharmacy Honor Society in 1994 and was awarded a Summer Research Fellowship award in 1995.

While in graduate school, the author's extracurricular activities included riding his Harley Davidson 850 miles to a Biker Rally in Menoken Grove in North Dakota the Summer of 1994, and also playing keyboards in a rock and roll band named "Barnacle Spöre". The band sounded good after about three beers and provided entertainment at several college parties.

The author met his future wife Suwanna Vangveravong after being assigned a desk and research space in the same laboratory, and the two worked together for two years before she received her Ph.D. degree in 1994 and returned to Bangkok, Thailand. The author participated in a foreign student exchange program based in Khon Kaen, Thailand in July-August 1995 entitled "Workshop, Field Study, and Scientific Excursion on Ethnobotony and Ethnopharmacology." This program included visits to medicinal plant gardens, government agencies, universities, and excursions into the rainforests of Northern Thailand (Chaing Mai area) to examine plant species, and also visits to the primitive Hilltribe Communities (Akha villages) including visits with Traditional Thai Healers ("Medicine Men"). He also met his future wife's family and obtained his future father-in-law's permission to marry Suwanna. The author and Suwanna were married in March 1996 in her father's home in Bangkok, Thailand.

The author received his Ph.D. degree in 1997 and moved to Bangkok to work in the area of isolation and characterization of anticancer compounds from natural sources at the Government Pharmaceutical Organization of Thailand.